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Acute Nonspecific Pericarditis

Clinical, Laboratory, and Follow-up Considerations

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Acute nonspecific pericarditis has been recognized with increasing frequency in recent years although there is reason to believe that it was considered distinct from rheumatic pericarditis almost 100 years ago. The authors have been able to secure follow-up information on 50 cases seen between 1930 and 1949. A few have shown persistent electrocardiographic changes, and calcification of the pericardium occurred in 1 case. In general the prognosis appears excellent and we have not observed constrictive pericarditis as a sequela.

IN RECENT years the syndrome of acute nonspecific pericarditis has stimulated the interest of clinicians in increasing degree. The frequency of this condition and its potential relationship to chronic constrictive pericarditis prompted us to review the experience with this form of pericarditis at the Massachusetts General Hospital. The study consists of two parts: a review of the clinical and laboratory aspects of this syndrome and a follow-up study of these patients. Fifty cases were reviewed whose acute illness occurred in the two decades from 1930 to 1949, and long-term observations were obtained on those patients whose illness antedated this study by more than two years.

HISTORICAL BACKGROUND

Ninety-six years ago there appeared in the Boston Medical and Surgical Journal a case record reported by Hodges entitled "Idiopathic Pericarditis," from which he drew the following conclusion: "Acute pericarditis is likely to occur from exposure to cold or when no exciting cause can be detected. . . ." The report described a 40 year old female patient at the Massachusetts General Hospital on the service of Dr. M. S. Perry, with complaints of left anterior chest pain, chills, fever, weakness, nausea, and palpitation. Physical findings were diagnostic of acute pericarditis with effusion, and the judicious application of several blisters to the thorax promptly resulted in a cure. The author noted the rarity of cases without associated rheumatism and declared that "the rapidity of recovery, the simple treatment, and the facility with which the effusion was dispersed are points to be specially remarked."[1]

The association of this form of pericardial reaction with an antecedent upper respiratory infection has been stressed. Credit for the initial case description demonstrating such a relationship is generally given to Comer,[2] but the conclusions of Hodges cited above and published in 1854 indicate that this relationship must have been appreciated many years ago. In 1906 Morison reported the case of a child with acute follicular tonsillitis in which acute pericarditis of benign nature was a sig-

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nificant finding.[3] In 1942 Barnes and Burchell reviewed the status of this syndrome.[4] Since then numerous case reports have appeared and the syndrome described under multiple designations including acute benign pericarditis, serofibrinous pericarditis of undetermined cause, pericarditis simulating coronary occlusion, cryptic pericarditis, and idiopathic pericarditis.[5–25]

Method and Clinical Description

The cases described in this review were assembled from the records of all cases of acute pericarditis occurring at the Massachusetts General Hospital and on the private services of Dr. P. D. White, Dr. H. B. Sprague, and Dr. E. F. Bland. All cases in which a specific etiology was ascertainable were excluded. Pericardial inflammation accompanying uremia, myocardial infarction, rheumatic carditis, purulent chest disease, tuberculosis, trauma, myocarditis, and endocrine imbalance was not included. Of the remaining cases, 50 fulfilled the requirements of acute nonspecific pericarditis and were submitted to clinical review and follow-up examination.

Table 1.—*Incidence*

1930–34	8 cases
1935–39	6 cases
1940–44	20 cases
1945–49	16 cases
Total	50 cases

Table 2.—*Incidence According to Age and Sex*

Age	Male	Female	Number of Cases
0–10	0	1	1
11–20	10	3	13
21–30	6	2	8
31–40	7	3	10
41–50	5	4	9
51–60	4	1	5
61–70	3	1	4
Totals	35	15	50

Review of these records indicates that acute nonspecific pericarditis has been more common during the recent years of the series. These data are summarized in table 1. Reports have indicated that this syndrome is most frequent in young adults. That this is not strictly the case is shown in table 2. It may be seen that a fair percentage of patients had acute pericarditis during the "coronary" period of life, and hence the patient's age cannot be depended upon in the differential diagnosis from myocardial infarction. The usual predominance of pericarditis in the male is found in this group of cases.

An upper respiratory infection or mild, nonspecific period of general malaise commonly precedes the onset of this form of pericarditis. In a recent series Levy and Patterson report 23 of 27 cases ushered in with upper respiratory infections.[22]

Table 3.—*Antecedent Respiratory Infection*

Description	Cases	Interval period in days
"Grippe"	7	1, 7, 8, 10, 14, 14, 30
"Cold"	7	2, 3, 5, 7, 14, 21, 60
"Pleurisy"	2	3, 30
"Upper respiratory infection"	9	5, 8, 10, 10, 10, 11, 14, 14, 40
"Acute bronchitis"	2	14, 30
"Cold and pneumonia"	2	4, 40

Of the 50 cases summarized in this report 29 had an antecedent respiratory illness and 21 failed to give such history. These data are summarized in table 3. It will be noted that in over one-half there was an interval of 7 to 14 days of partial or complete freedom from symptoms prior to the onset of the complicating pericarditis. In only one instance was a patient so ill that hospitalization during the interim was necessary. Among the patients in whom an episode of previous illness was not elicited, it was not infrequent for the pericarditis to occur following unusual physical or emotional exertion, or exposure to cold.

Five patients gave a history of known contact with active tuberculosis, and the number of cases with a personal or family history of allergy was high.

The onset of pericarditis was described as occurring abruptly in 25 instances and less acutely in 25. By far the most common present-

ing complaint was pain with 46 of the 50 cases (92 per cent) listing this as the initial symptom.

The pain was generalized over the entire anterior chest in 17 cases, restricted to the mid-chest and substernal area in 18, limited to the left shoulder in 6, to the left anterior chest in 3 and the right anterior chest in 2, and over the abdomen in 1. The pain was intensified by respiration in 35 patients (76 per cent), by change in position in 5, and by cough in 2. Pain was aggravated by the prone position in 7 cases. The patients described the pain as severe in 19 cases, moderate in 24, and minimal in 3. In 34 instances it was intermittent, but was continuous in 14.

There was no consistent description of the discomfort. A galaxy of terms was used by the patients to describe their distress and the most commonly used terms included: sharp, dull, aching, pressing, gripping, constricting, and tightness. The variable nature of the pain and the difficulty of differentiating it from the pain of other cardiac and pulmonary diseases is readily apparent.

TABLE 4.—*Radiation of Pain*

Left shoulder	19	Epigastrium	3
Right shoulder	9	Back of neck	2
Neck	7	Jaw	1
Back	6	Elbows	1
Costal margins	4	Right chest	1
Left arm	4		

Radiation of the pain was common, and the locations are listed in table 4. Dyspnea was the initial symptom in 2 instances and fever in 2.

Collateral or subsequent symptoms appearing during the acute illness are listed in table 5. Malaise, fever, cough, and dyspnea were noted to be the most common accompanying complaints. Signs of circulatory collapse were infrequent.

The physical finding of greatest significance in the diagnosis of this illness is a pericardial friction rub. Its presence within a few hours of the onset of chest pain is a valuable aid in the differentiation of this syndrome from acute myocardial infarction, where such a sign seldom appears within the first 36 hours. In some instances a pleuropericardial element is present. In 37 patients of this group a friction rub was heard. This figure is lower than might be anticipated in cases selected purely from a hospital population. Several of the patients in this series were seen in consultation after the period of probability of a friction rub had diminished. All degrees of loudness were described, and in 30 cases the rub was heard on the initial visit of the physician. The mean duration of the rub was 9 days, with an extreme of intermittent appearance for 60 days in 1 patient. A loud to-and-fro rub was fairly consistently associated with a more prolonged course than a poorly discernible friction sound.

Enlargement of the cardiac shadow was found in 25 instances. This was attributed to pericardial fluid in 3 cases and to cardiac dilatation in the remainder. The assumption that the cardiac enlargement was due to dilatation rather than fluid was based upon the lack of suppression of cardiac sounds, absence of signs of cardiac compression, and persistence of normal voltage in the electrocardiogram. It has been stressed that a dilated heart may mimic pericardial effusion so closely that the roentgenologist is unable to establish the differential diagnosis. Without angiocardiographic studies or diagnostic pericardial aspirations, only a presumptive conclusion is possible.[27, 28]

TABLE 5.—*Collateral Symptoms*

Malaise	49	Palpitation	3
Fever	49	Ankle edema	2
Cough	19	Night sweats	2
Dyspnea	18	Numbness of arms	2
Nausea	6	Collapse	2
Anorexia	5	Dizziness	1
Chill	4	Headache	1
Orthopnea	4	Cyanosis	1
Vomiting	3	Insomnia	1

Pleural fluid was also noted in 14 instances and the chest x-ray examination indicated bilateral effusion in 6, isolated left-sided fluid in 7, and isolated right-sided effusion in 1 instance.

Albuminuria was observed in 2 cases. Tuberculin skin tests were performed on 12 patients. The result was negative in 8 instances and revealed a minimal response in the remaining 4 cases. Where sedimentation rates were obtained, all but 3 were elevated, and this test proved an accurate index of improvement in

the clinical status of the patient. A moderate normocytic anemia was observed in 8 of 37 patients in which hematologic studies were performed.

Blood, urine, throat, and nasal cultures were obtained in several instances but no consistent findings were observed. The duration of the acute illness was very variable with extremes of 2 to 70 days. The mean duration of illness was 13 days. Treatment was supportive and no specific effect was noted when penicillin, sulfonamides, or salicylates were used.

The electrocardiogram is a valuable diagnostic aid in many cases of acute pericarditis, and this has been the subject of a number of excellent reviews.[29–34] Changes in the T wave following trauma to the pericardium were initially observed by Barnes and Mann in 1932, and the initial concept that such changes are due to subepicardial myocardial damage stems from a report by Fowler, Rathe, and Smith, published the next year.[35, 36] Following this work pericarditis was the subject of numerous electrocardiographic observations.

The electrocardiographic pattern depends upon several factors, including the phase of the pericarditis, degree of subepicardial damage, amount of pericardial effusion, and adequacy of electrocardiographic exploration. Unquestionable cases have been reported without electrocardiographic changes, and in such instances it must be assumed that the integrity of the myocardium has been so minimally disturbed that RS-T changes did not occur.

RS-T segment elevation may be quite evanescent and was not observed after the twelfth day. Nay reports an interesting differential point from myocardial infarction, observing that in pericarditis the T-wave negativity seldom appears until the RS-T segment has returned to the isoelectric line.[34] Late electrocardiographic changes will be considered in a subsequent part of this paper.

Long-Term Observations

In spite of the extensive literature devoted to the clinical findings in acute nonspecific pericarditis few reports have included data describing possible late effects of this condition. Burchell indicates that he is following a number of cases and Levy recently reported 17 patients who had been observed two years or more after the initial episode.[17, 22] To our knowledge no instance of chronic constrictive pericarditis has occurred in the follow-up observations of the reported cases.

Forty-seven instances of acute pericarditis had occurred more than two years prior to follow-up and their subsequent course was reviewed. Since 2 patients had been hospitalized on two occasions with similar findings the actual number of patients was two less than the number of episodes of pericarditis, making a total of 45 patients and 47 instances of pericarditis concerned in the follow-up.

Table 6.—*Duration of Follow-up*

Years	*Patients*
0–4	12
5–9	19
10–14	6
15–18	6

Table 7.—*Present Ages*

0–10	0	41–50	13
11–20	3	51–60	5
21–30	7	61–70	4
31–40	8	71–80	1

Information was available on all but 4 of these individuals. Twenty-nine patients were seen and examined in this hospital and 9 were examined for us by competent internists elsewhere. Partial information was available in 2 instances, and 1 patient had expired. The duration of the follow-up and present ages of the patients are summarized in tables 6 and 7. All living patients were able to carry on normal activity and many were engaged in strenuous vocations.

Because of the frequency of recurrences in this syndrome the term "acute relapsing pericarditis" has been used.[17] Two of our patients gave a history compatible with previous acute pericarditis when seen, and 4 more suffered recurrences (14.6 per cent). In addition there were 3 other patients in which a recurrence was suspected, but evidence was not conclusive. Four recurrences each were noted by 2 patients. In general recurrences were of less intensity and of shorter duration than the initial illness. Chest

pain, fever, and malaise were the common symptoms and were quickly recognized by the patient as being similar in nature to his first episode.

A further group noted transient bouts of sharp, stabbing left chest or shoulder pain unattended by fever, malaise or abnormal physical findings. Ten patients (24.4 per cent) were so afflicted and in 5 it was a distressing symptom. This pain frequently was related to deep breathing but was not associated with exercise and was unaccompanied by dyspnea. Characteristically the pain appeared at intervals and the patient would be symptom free for progressively greater periods as time passed. One patient described continuous dull left anterior chest discomfort for several years after his acute illness.

Three patients complained of diminished strength following the illness, and 5 patients dated the onset of nervousness to this event. Two patients were moderately incapacitated by a cardiac neurosis. Two individuals noted exertional dyspnea and 3 complained of a minimal ankle edema in the evenings.

During the interim between the initial illness and this examination 5 patients had had pneumonia. Five considered themselves highly susceptible to virus infections and 6 had recently been in contact with a person with pulmonary tuberculosis. Sixteen patients (39 per cent) gave a personal history of allergy and 6 others (14.6 per cent) had a high familial incidence of disease commonly attributed to an allergic background.

In general it may be stated that the majority of patients were in excellent health. General physical examination indicated severe rheumatoid arthritis in 1 case, and signs compatible with a mild virus pneumonitis in another. Seven patients were moderately obese.

Three patients had developed hypertension and moderate cardiomegaly was observed in 4 instances. In 3 of the latter cases no adequate explanation was ascertainable. Six patients (14.6 per cent) had functional systolic murmurs, and 2 patients had murmurs of grade II intensity at the apex which were unexplained and probably without significance. Bilateral basal pulmonary rales were observed in 1 instance to be described more fully subsequently. The patient who expired died of chronic hypertensive cardiovascular disease which had been present for years prior to the episode of acute pericarditis.

Residual abnormalities in the electrocardiogram following acute nonspecific pericarditis have not been reported. It has been assumed in the past that the record always returned to a normal pattern.

In 6 instances among our cases significant abnormalities were observed which were unexplained by other cardiac or systemic disease. Four patients showed a low voltage or isoelectric T_1 associated with an inverted T in aV_L, and reversal of the T_1/T_3 ratio (fig. 1). In one of these cases T waves were inverted in leads I, II, III, aV_F, V_3, V_4, V_5 and V_6 (fig. 2). Two additional cases revealed low voltage complexes in leads I and aV_L. One of these latter cases was associated with a diphasic T_2, low voltage T wave in V_5, and isoelectric T in V_6 (fig. 3). Serial records are available on this patient and indicate the apparent permanency of the pattern.

Minor deviations from the normal were observed in several other cases. Four patients had a left axis deviation and 1 a right axis deviation. In 2 the A-V conduction was prolonged to 0.22 and 0.26 second; however, these were elderly patients and this may have represented "normal" variant. A poor axis shift with change from the left to the right lateral recumbent position was observed in 3 instances. Standard two step exercise tests were performed on a majority of cases and no significant deviations from the resting record were observed.

Residual roentgenologic pulmonary or cardiac changes have not been reported in cases of acute nonspecific pericarditis. The patients observed in this hospital during follow-up examinations were fluoroscoped and posteroanterior, posteroanterior grid, and lateral chest films were obtained. When indicated special spot films and oblique views were taken. The films were interpreted by the Department of Radiology. In the patients studied elsewhere a report was obtained. Two were in the military service and chest x-rays were assumed to be within normal limits.

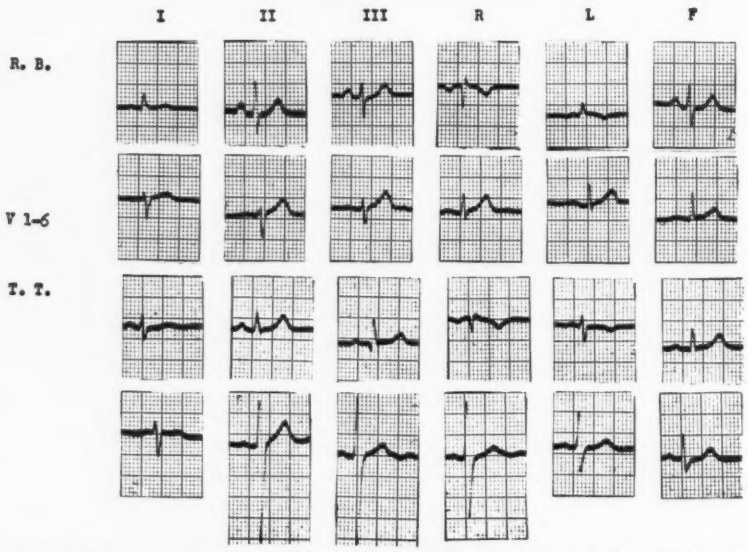

FIG. 1. Two examples of residual low voltage of T_1 and inverted T in aV_L. In the lower tracing (T. T.) the semivertical electrical position of the heart may be partially responsible for these changes.

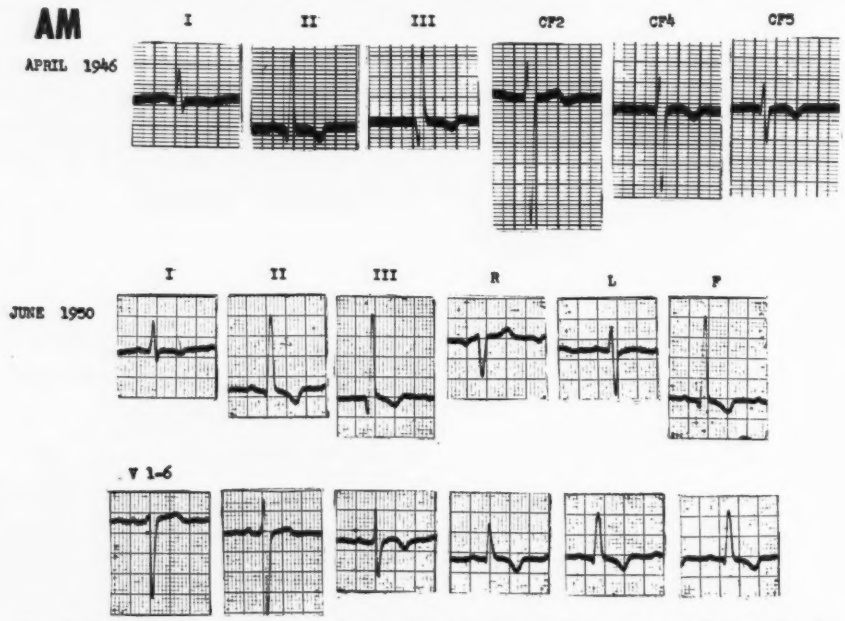

FIG. 2. Residual electrocardiographic abnormality in case showing pericardial calcification on x-ray.

X-ray follow-up examination was made on 37 of the 41 patients. In this group were 3 patients with apparent left ventricular enlargement, and 6 more cases in which the left ventricle was noted to be prominent without cardiac enlargement. In 1 case to be described in detail subsequently there was calcification of the pericardium. Three cases gave evidence

of old pleurisy and in another x-ray findings coincided with the clinical impression of pneumonitis.

The following case report is of interest:

A. M., female, age 54. Four years ago this patient developed an upper respiratory infection which was abating when she experienced the gradual onset of generalized chest pain of moderate severity, radiating to both shoulders. It was intermittent and markedly aggravated by deep inspiration. She noted some relief in a semirecumbent position. Night sweats were a prominent feature of the illness. There was no dyspnea and although she did not record her temperature, she did not feel feverish. She had no cough and her appetite was fairly well maintained during the illness. Except for occasional rest periods she carried on her housework for several days before consulting her local physician who examined her and referred her to one of us (E. F. B.).

There was no past history of disease of the cardiac or pulmonary systems, and nothing to suggest a previous episode of myocardial infarction or angina pectoris. Her health had always been vigorous, and except for an abdominal operation 11 years previously she had been well.

Physical examination revealed her to be somewhat obese and in no distress. Inconstant pulmonary rales were noted in the lung bases but other physical findings were within normal limits. The blood pressure was 140/85 and no friction rub was elicited. Fluoroscopy revealed slight fullness of the left ventricle and minimal haziness in the left lung base, compatible with a resolving pleuritis. No calcification of the pericardium was observed. The electrocardiogram was abnormal and is reproduced in figure 2. A diagnosis of nonspecific pericarditis was made.

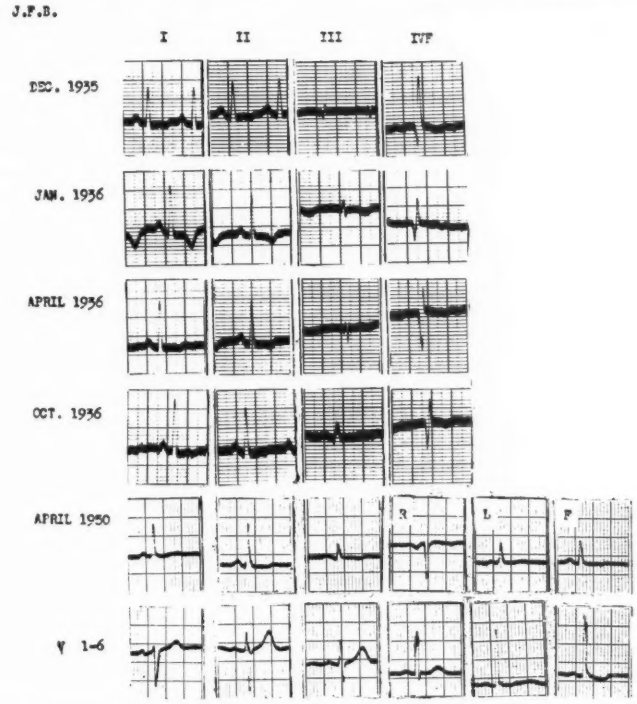

FIG. 3. Serial records showing residual electrocardiographic changes. In the first four tracings note inverted lead IV, as compared with the convention of today.

In the interval period of four years this patient had been well and active. She managed a household and carried on a full and normal life. Her only complaint was intermittent sharp chest pain located over the cardiac apex and unrelated to exertion or emotion. Her weight was maintained and she had no edema, exertional dyspnea, cough, or hepatic tenderness. She stated that she sleeps on two pillows but attributes this to habit.

Follow-up physical examination four years later revealed her to be moderately obese, with a blood pressure of 140/80 and pulse of 68. The left cardiac border coincided with the left midclavicular line. No thrill was detected. The second aortic exceeded the second pulmonic sound. In recumbency at the pulmonary area an inconstant grade I systolic murmur

was detected. At both pulmonary bases moist rales were heard in all phases of respiration and were not cleared by coughing. The liver and spleen were not palpable. The neck veins were normal, and there was no ankle or sacral edema.

Fluoroscopy and x-ray films revealed cardiac enlargement chiefly in the region of the left ventricle with a cardiothoracic ratio of 15.5/29 cm. Calcification was noted surrounding the apex of the heart in the region of the anterior-inferior aspect of the left ventricle. It was the impression of the fluoroscopist that this region pulsated with diminished amplitude (fig. 4).

FIG. 4: Posteroanterior chest film demonstrates a thick ring of calcium encasing the anterior-inferior aspect of the left ventricle.

It is most unfortunate that this patient was not observed earlier in the initial phase of her illness. Her lack of early electrocardiograms, x-ray studies, and postponement of medical assistance until the acute phase had subsided forces us to accept with considerable reservation a conclusion that only acute nonspecific pericarditis could be the cause of the residual changes observed at the present time. It is entirely possible that a minor amount of pericardial calcification could have been missed fluoroscopically at the first visit.

At the present time the only indication of pericardial disease is found in the x-ray examination. Physical findings have not appeared and she must be considered to have healed pericardial disease which is not producing symptoms.

ETIOLOGIC CONSIDERATIONS

Descriptions of the syndrome of acute nonspecific pericarditis appearing subsequent to the paper by Barnes and Burchell have added little to the clinical pattern, and in nearly all instances their contentions have been verified. The problem of etiology, however, has remained unsolved. The prevailing hypotheses include: *a*, virus infection of the pericardium; *b*, tuberculous infection of the pericardium; *c*, pericardial response to unknown toxins and *d*, hypersensitive response of the pericardium. Proponents of the concept of a virus infection point to the history of epidemics of pericarditis, the relationship to virus infection of the upper respiratory passages, absence of bacterial flora in cultures of pericardial fluid, benign course, and, more recently, evidence supporting response to aureomycin.[23] As yet unproved, this theory lacks the support of a controlled experiment with antiviral agents. An adequate explanation of the usual lag between infection of the respiratory system and pericarditis has not been forthcoming; and the characteristic leukocytosis has no counterpart in known viral pulmonary infections.

Because of the known frequency of tuberculous infection of the pericardium, suspected relationship with chronic constrictive pericarditis, and reports of pericarditis during the appearance of the Ghon complex, tuberculosis has been suspected as the cause for acute nonspecific pericarditis. Pericarditis, particularly when accompanied by effusion, has been deemed similar to idiopathic pleurisy with effusion in the young adult. For years such pleural effusions have been considered tuberculous but proof has not always been forthcoming.

It is certainly true that the syndrome of acute nonspecific pericarditis bears little similarity to the description we accept as representing primary tuberculous pericarditis. Clinically primary tuberculous pericarditis was described originally by Riesman in 1901 and numerous reports substantiating his conclusions have appeared in subsequent years.[37–3]

With few exceptions authors agree that this disease is notable for the infrequency of complaints referable directly to the chest. Chest pain is an uncommon symptom and is a particularly uncommon presenting complaint, appearing in but 1 of 13 cases reviewed by Clarke.[40] Stepman and Owyang noted chest pain in 35 per cent of their cases, but this symptom was overshadowed by fever (89 per cent), shortness of breath (76 per cent), edema (68 per cent), cough (51 per cent), and weakness (43 per cent). The physical findings, laboratory results, and prolonged, unfavorable course serve further to distinguish this disease from acute nonspecific pericarditis.[41] Pericardial effusion occurs in the majority of instances and distended neck veins, pleural effusion, palpable liver, and cardiac arrhythmias are common. The leukocyte count is seldom elevated. Unless we radically revise our concepts of primary tuberculous pericarditis, there seems little chance for confusion.

A response to unknown toxins by the pericardium has been suggested. To date no definitive evidence has appeared which would support this concept, except for the known frequency of pericarditis in terminal uremia.

A hypersensitive response by the pericardium has been postulated to explain many forms of pericarditis.[8, 42–47] Reports have appeared of pericarditis clinically indistinguishable from the acute nonspecific form occurring during serum sickness.[48] In isolated case reports eosinophilia has been noted and fluid with high eosinophil counts has been recovered by pericardial and pleural aspiration. In 1 such case prompt recovery attended administration of an antihistamine compound.[47] Partially elucidated by such an hypothesis would be the acute pericarditis which appears as an incidental finding in a diversity of afflictions. There is no question but that the pericardium may act as a 'shock' organ in a form resembling acute nonspecific pericarditis, although there is no definitive evidence indicating that this is a frequent event.

Differential Diagnosis

The differential diagnosis of acute nonspecific pericarditis includes other clinical entities causing chest pain and a friction rub. Of predominant importance is the recognition of this syndrome from acute myocardial infarction. Although shock, circulatory collapse, and fear of impending death are infrequent in acute pericarditis, the clinical resume reveals that they may occur. The early appearance of leukocytosis, fever, and a pericardial friction rub aid in recognition of pericarditis. Pain with respiration is uncommon in acute myocardial infarction. Early and adequate electrocardiography also aids in differentiating the two.

Acute rheumatic pericarditis may antedate other clinical signs of acute rheumatic fever. Endocarditis is ultimately manifest in most instances and the diagnosis is clarified.

Other causes of acute chest discomfort, such as dissecting aneurysm, angina pectoris, diaphragmatic hernia, spontaneous pneumothorax, mediastinal emphysema, acute pleurisy, and so forth, seldom cause difficulty after preliminary physical and laboratory examination.

Relationship to Chronic Constrictive Pericarditis

In reviewing a series of patients with chronic constrictive pericarditis a history of acute pericarditis, acute pleurisy, or severe respiratory infection is not infrequent. Paul, Castleman, and White obtained a history of pericarditis in 4 of 53 cases, and 2 further patients had been afflicted with pleurisy.[49] Blalock and Burwell note that a certain number may have antecedent respiratory infection.[50] In Kelly's classic review of polyserositis with chronic pericardial changes 5 cases of 39 gave a history suggestive of previous acute pericarditis, (cases of Mott,[2] 1887; Feierabend, 1866; Rumpf, 1895; and Heidemann, 1897).[51–55] Nicholls reported 13 cases, and in 2 acute pericarditis had occurred.[56] Isolated case reports have recorded similar findings.

Realization of this fact has led clinicians to have some reservation in stating an entirely optimistic prognosis for patients with acute nonspecific pericarditis.

Analysis of these case reports indicates that in the majority of instances signs of cardiac compression appeared soon after the initial

pericarditis. In 3 of the 4 cases reported by Paul and associates, the onset was a matter of months. Mott's 2 cases noted symptoms seven months after the acute episode, and the cases reported by Rumpf and Heidemann had only a short interval of normal health. In this group, only 1 case reported by Paul and coworkers and that reported by Feierabend enjoyed good health for an appreciable period. Although such acute pericarditis may be indistinguishable from acute nonspecific pericarditis, further analysis of cases appearing in the literature indicates that it is rare for this to be true. In the usual instance the initial complaints are more commonly dyspnea and weakness, and chest pain is not stressed. Such cases fit the picture of primary tuberculous pericarditis more closely in some respects than the nonspecific form.

Among the 41 patients observed for a period greater than two years there was only one in whom a suggestion of chronic changes appeared to be legitimate.

Summary

1. Fifty cases of acute nonspecific pericarditis have been reviewed with special reference to clinical, laboratory, and follow-up considerations.

2. The prevailing theories of causation of this syndrome have been summarized and discussed.

3. Long-term follow-up examinations on this group indicate an excellent prognosis, although residual electrocardiographic abnormalities are not infrequent.

4. Pericardial calcification is present in only 1 patient and fluoroscopy reveals a diminution in the amplitude of cardiac contractions, but there is no evidence of impaired function.

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Effect of Choline upon Experimental Canine Arteriosclerosis

By J. D. Davidson, M.D., Walter Meyer, M.S., and F. E. Kendall, Ph.D.

Studies have been made of the effect of excess dietary choline upon the arteriosclerosis produced in dogs by a regimen of cholesterol and thiouracil feeding. The choline-fed animals did not differ significantly from the control animals with respect to serum lipid levels, degree of lipid infiltration of their livers or severity of arteriosclerotic involvement.

CHOLINE is currently being promoted for the treatment of human arteriosclerosis. Its use is based upon certain theoretic considerations, upon limited clinical experience, and upon observations of its effect in preventing and curing experimental arteriosclerosis in animals. It has been postulated that since choline has powerful lipotropic activity in preventing the development of certain types of fatty deposition in the liver and kidneys, and in accelerating the removal of fat from these deposits after they are formed, it should also be effective in preventing and curing arteriosclerotic deposits. However, choline is most effective in curing conditions caused by the ingestion of diets deficient in choline. It has little effect on fatty livers caused by feeding cholesterol, or on fatty livers resulting from mobilization of lipid from body deposits.[1] It has also been suggested that choline may have a specific "catalytic" role in the metabolism of lipids,[2] although such a function has never been demonstrated. A third theoretic basis for the use of choline is derived from the concept that the stability of cholesterol in serum may be important in the pathogenesis of arteriosclerosis. Most of the cholesterol in normal human serum is held in solution by being part of lipoprotein molecules which contain protein, cholesterol, cholesterol esters, and phospholipids.[3] Since choline is a constituent of some phospholipids its administration might contribute to phospholipid formation and thus to stabilization of serum cholesterol.

Regardless of possible theoretic bases for the use of choline in the treatment of arteriosclerosis, the final decision as to its value must be made on the basis of its actual effect upon the disease. The impossibility of quantitation of human arteriosclerosis makes evaluation of clinical data difficult. Evidence of its value in experimental arteriosclerosis in animals is inconclusive and conflicting. Reports that choline is effective in delaying or preventing the development of atheromatous lesions in cholesterol-fed rabbits and chickens[4-6] have been contradicted by other workers using the same species and similar technics.[7-9] For this reason the influence of choline upon the development of experimental arteriosclerosis in a third species, the dog, has been studied.

Dogs share with human beings the ability to dispose of large amounts of dietary cholesterol without developing excessively high serum cholesterol levels. However, when the function of the thyroid is depressed by daily thiouracil administration extremely high cholesterol levels can be maintained as long as cholesterol is fed.[10, 11] Upon withdrawal of the cholesterol and thiouracil the serum cholesterol falls to normal levels within a few days. The feeding of 10 Gm. of cholesterol per day to a dog weighing 10 Kg. will increase its serum cholesterol from a level of 100 to 200 mg. per 100 cc. to a level that averages around 400 mg. per 100 cc. The daily administration of 0.6 to 1.2 Gm. of thiouracil alone will increase

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the serum cholesterol to the same level. When both cholesterol and thiouracil are given, cholesterol levels averaging around 1000 mg. per 100 cc. can be maintained, with some dogs showing occasional levels as high as 4000 to 5000 mg. per 100 cc. Although much variation is found in the degree of arteriosclerosis produced in individual dogs by this regimen, the results on a series of 40 dogs[12] show that a fair correlation exists between the degree of hypercholesterolemia sustained over a definite period of time and the lesions produced. In studies of dogs maintained on the regimen for 1, 2, 4, 6 and 12 months, the 4 month period was found to be the shortest time to yield consistent and definite gross arteriosclerosis in all animals.

During the time required to accumulate this necessary information a pilot experiment lasting 12 months was run upon 3 dogs to determine the maximum amount of choline they would tolerate and to obtain information on the magnitude of the effect of choline upon the development of the lesions. Later a four month experiment, designed to test the effect of choline upon early minimal lesions, was run upon 14 dogs.

Methods

Three litter-mate female dogs of collie type were used for the 14 month experiment. The dogs weighed about 50 pounds and were 1 year old at the start of the experiment. They were housed in indoor cages and individually fed 1.2 Gm. thiouracil daily. Their diet consisted entirely of Spratt's no. 34 kibbled dog cakes. The daily 10 Gm. dose of cholesterol was fed in 200 Gm. of cholesterol-treated ration prepared by dissolving the cholesterol in ether, mixing it with the dog food and allowing the ether to evaporate. The cholesterol thus was distributed throughout the food in finely divided form. The cholesterol-treated ration kept well and large quantities could be prepared at one time and stored. Choline was administered by mixing a 50 per cent solution of choline hydrochloride with the ration. A dosage of 10 Gm. choline hydrochloride per day was found to produce persistent diarrhea in all dogs. The dose was diminished gradually and finally it was found that 5 Gm. was the maximum amount tolerated, producing only mild bouts of diarrhea that did not require reduction of dosage. After the cholesterol and choline-treated ration had been eaten, supplementary feedings of untreated food were given.

At the time of the later four month experiment a dog farm had been established. The 14 young, mongrel dogs used were housed there in groups with free access to outdoor runways. The dogs used were 4 months old at the start of the experiment and averaged under 20 pounds in weight. All were fed, ad libitum, the same 5 per cent cholesterol diet used in the 14 month experiment and were individually given 0.6 Gm. of thiouracil daily. Eight of the dogs were carried on this basic regimen as controls while 6 dogs received choline hydrochloride

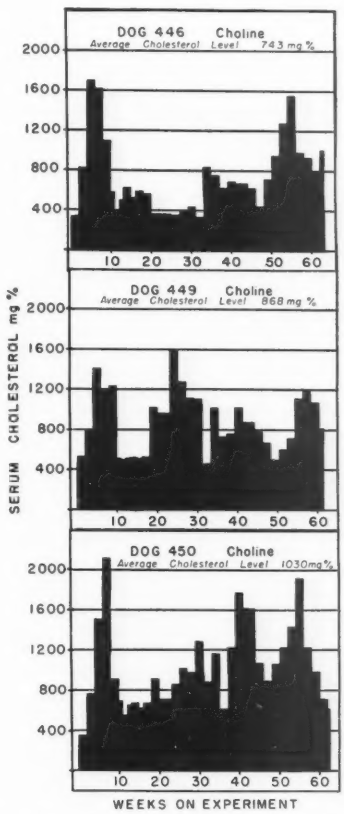

Fig. 1. Serum cholesterol levels of dogs fed cholesterol, thiouracil and choline for 14 months.

mixed with their food in an amount equal to 2.5 per cent of the diet.

Throughout both experiments blood samples were taken on all dogs every two weeks for lipid analysis. Serum cholesterol was determined by the method of Schoenheimer and Sperry[13] on all sera. Lipid phosphorus determinations were done by the method of Fiske and Subbarow[14] on petroleum ether extracts of evaporated Bloor filtrates from sera.

At the conclusion of both experiments all dogs

were sacrificed by the intravenous injection of sodium pentobarbital, and complete autopsies were performed. Routine sections of liver, spleen, kidney and numerous arteries were stained with hematoxylin and eosin and with oil red "O" for microscopic examination.

The livers of the four month dogs were analyzed for lipid content. Each liver was finely ground in a Waring Blendor. Duplicate samples of the resulting homogenates were dried to constant weight at 110 C. Other duplicate samples weighing between 6 and 12 Gm. were treated with 20 volumes of 3:1 alcohol-ether and allowed to stand at 5 C. for several days. They were then filtered through filter thimbles and extracted in Soxhlet extractors for 20 hours with fresh 3:1 alcohol-ether. The filtrate and extract were mixed and evaporated almost to dryness in a stream of nitrogen. This residue was repeatedly extracted with hot petroleum ether (boiling point, 68 C.). Aliquots of the extract were analyzed for total and free cholesterol and for lipid phosphorus by the methods used for serum, while total lipid was estimated gravimetrically.

Results

The 3 dogs in the 14 month pilot experiment developed hypercholesterolemia to a degree quite comparable with that seen in 5 dogs previously studied on the same cholesterol-thiouracil regimen without added choline[10, 11] (fig. 1). At autopsy all 3 dogs were found to have extensive and severe gross arteriosclerosis. The type, distribution and severity of the lesions in these animals were the same as had previously been observed in dogs receiving no added choline. All stages in the development of the lesions were represented. Some old plaques contained areas of calcification and hemorrhage. The choline had not prevented the deposition of fat within the hepatic parenchymal cells or other organs.

The four month experiment was undertaken because it seemed possible that the effect of

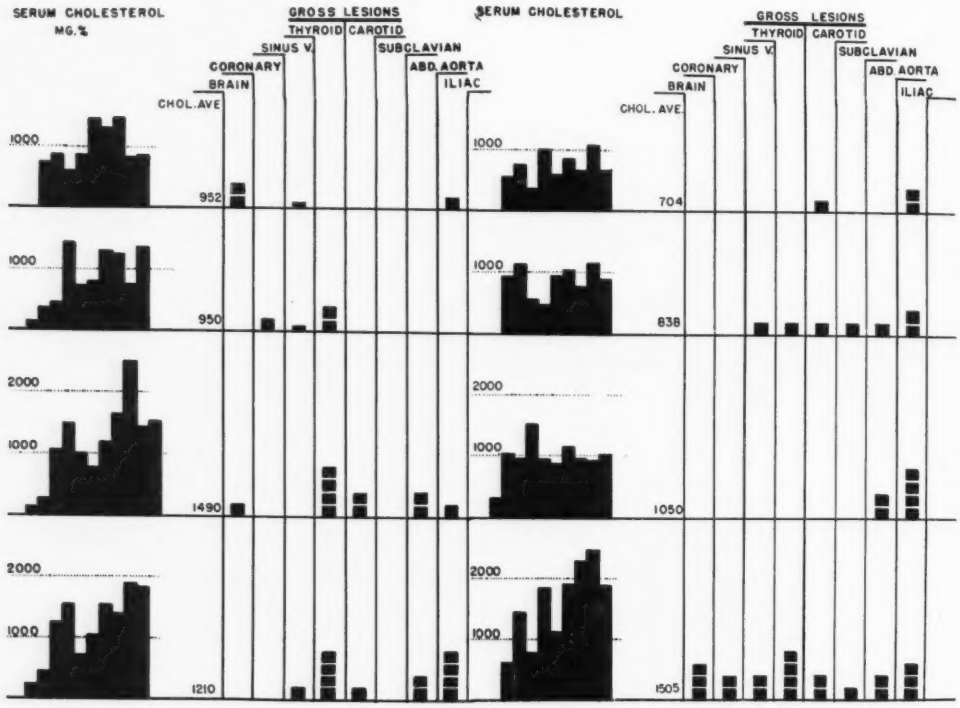

Fig. 2. Control dogs fed cholesterol and thiouracil for four months. Each bar on cholesterol graphs represents a two week period with average serum cholesterol level for the four month period indicated on right. The severity of the gross arteriosclerosis in each of eight sites is indicated by blocks on a scale of 0 to 4 plus.

choline might have been masked by the long exposure to the arteriosclerosis-producing regimen in the above experiment. The relation between the amounts of cholesterol and choline fed these animals was the same as in the pilot 14 month experiment. These animals were compared with 8 control dogs kept on the cholesterol-thiouracil regimen without added choline for four months. Four of the control dogs were on experiment concurrently with the choline-fed animals. Two were started on experiment six weeks earlier than the choline-fed dogs and the 2 remaining ones had been studied previously. Objectively the choline-fed dogs were indistinguishable from the 8 control dogs throughout the four month experiment. The food intake, the weight gain, the activity and general behavior were the same for the two groups.

The serum cholesterol levels during the experiment and the degree of arteriosclerosis at autopsy in these two groups of dogs are summarized in figures 2 and 3. When dogs of similar average cholesterol level from the choline and control groups are matched, the incidence and extent of the lesions are seen to be about the same in the two groups. Figure 4 shows the correlation between average serum cholesterol level and degree of arteriosclerotic involvement, a value obtained by summation

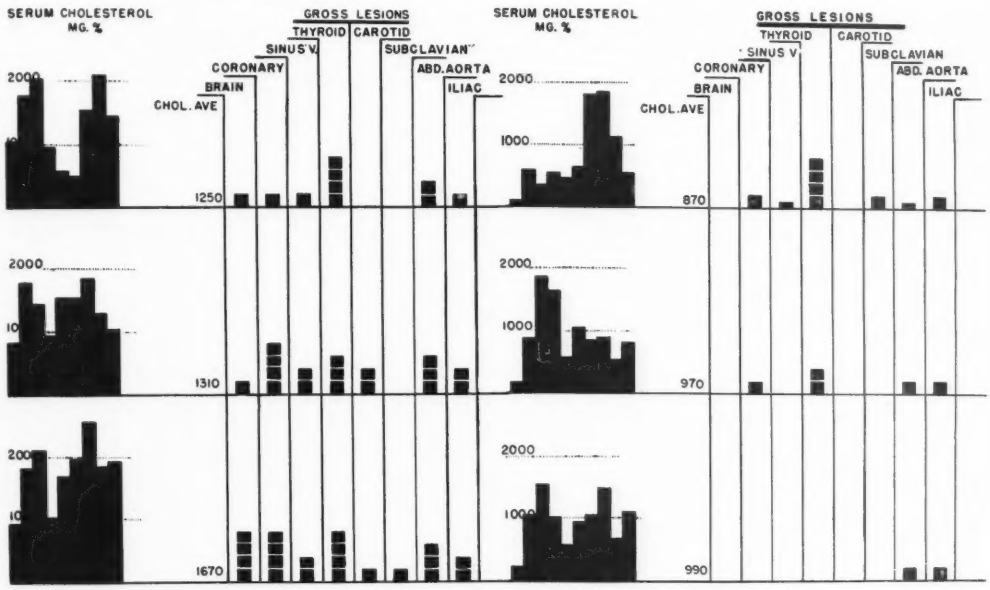

FIG. 3. Dogs fed choline in addition to basic cholesterol—thiouracil regimen for four months. See explanation under fig. 2.

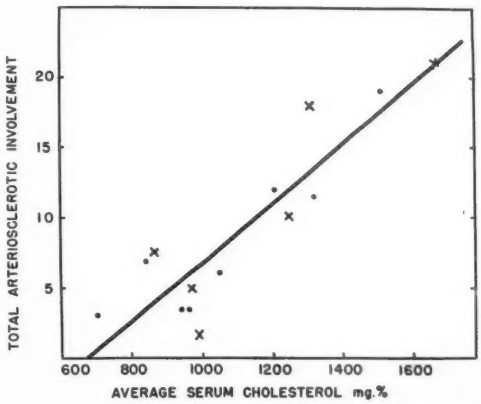

FIG. 4. Correlation between average serum cholesterol level and gross arteriosclerosis in dogs on regimen for four months. Total arteriosclerotic involvement is the sum of the severities of lesions in the eight sites tabulated in figures 2 and 3. Each dot represents a control dog and each X a dog which received choline.

of the severities of lesions in the eight arteries listed in figures 2 and 3. There was no significant difference between the two groups.

serum from each dog were analyzed for both lipids. Previously in this laboratory 351 samples of serum from dogs on the basic

TABLE 1.—*Effect of Excess Dietary Choline upon the Serum Cholesterol: Lipid Phosphorus Relationship*

Dog No.	Total Cholesterol	Lipid Phosphorus			Dog. No.	Total Cholesterol	Lipid Phosphorus		
		Found	Calculated*	Δ			Found	Calculated*	Δ
2.5% Choline Hydrochloride Added to Diet									
	Mg. %	*Mg. %*	*Mg. %*	*Mg. %*		*Mg. %*	*Mg. %*	*Mg. %*	*Mg. %*
33	880	33	29	4	34	820	28	28	0
	1640	34	42	−8		1450	33	39	−6
	1040	33	32	1		1540	41	40	1
	860	31	28	3		1860	46	46	0
	520	27	22	5		1290	35	36	−1
35	1020	33	31	2	36	620	22	24	−2
	1010	26	31	−5		560	20	23	−3
	930	33	30	3		630	30	24	6
	1470	43	39	4		1880	49	46	3
	680	26	25	1		1150	36	33	3
						540	23	23	0
37	1020	32	31	1	38	940	32	30	2
	2020	49	49	0		2110	51	50	1
	560	27	23	4		1680	45	43	2
	1540	42	40	2		2550	53	58	−5
	2110	52	50	2		1850	51	46	5
	1440	43	39	4		1940	48	47	1
No Choline Added to Diet									
6	1530	43	40	3	10	1550	42	40	2
	960	31	30	1		720	24	26	−2
	890	33	29	4		1060	33	32	1
	1170	34	34	0		1550	39	40	−1
	950	30	30	0		1380	36	38	−2
	940	29	30	−1		1900	41	47	−6
	1040	34	31	3		1840	42	45	−3
29	1500	39	40	−1	30	1420	42	38	4
	790	25	27	−2		810	24	27	−3
	1660	38	42	−4		1380	34	37	−3
	1460	35	39	−4		760	26	27	−1
40	910	34	29	5	41	570	27	23	4
	940	33	30	3		410	19	21	−2
	770	24	27	−3		590	23	24	−1
	910	36	29	7		670	24	25	−1
42	620	29	24	5		660	25	25	0
	750	24	26	−2	43	730	34	26	8
	1120	30	33	−3		570	23	23	0
	2270	54	53	1		1430	44	38	6
	2460	53	56	−3		1480	35	39	−4
	2080	50	50	0		850	30	28	2

* P = 13.34 + 0.0175 cholesterol.

Studies were made of the serum cholesterol and serum lipid phosphorus in both control and choline-fed dogs. Four to seven samples of

cholesterol-thiouracil regimen have been analyzed by these methods and the serum lipid phosphorus has been found to rise in an

orderly manner with increasing serum total cholesterol.[15] The relationship, *Lipid Phosphorus (mg. per cent) = 13.34 + 0.0175 × Serum Cholesterol (mg. per cent)*, is maintained throughout the range of serum cholesterol from 300 to 5000 mg. per 100 cc. with a standard error of the estimated phosphorus at a given cholesterol, equal to 4.37 mg. per 100 cc. Table 1 shows the values found for the serum cholesterol and lipid phosphorus in both the choline-fed and the control dogs, together with the lipid phosphorus value calculated for each cholesterol from the above equation. In the control dogs the average difference between the found and calculated phosphorus values is +0.17 mg. Fifty per cent of the values found are lower than those calculated. In the choline-fed dogs the mean difference between the found and calculated phosphorus values is +0.91 mg. and only 21 per cent of the thirty-three determined values are lower than the calculated values. The regression line calculated by the method of least squares for the interrelationship of these two lipids in the choline-fed dogs is: *Lipid Phosphorus = 15.67 + 0.0163 × Cholesterol*. The difference between the two constants in this equation and the corresponding values in the equation for the large series of dogs not fed choline is not statistically significant.

At autopsy no evidence was found of any lipotropic action of choline upon the livers of these dogs. Microscopic examination showed the same degree of fatty infiltration of the livers in the choline-fed and the control dogs. Chemical analysis of the livers confirmed this. Table 2 gives the values found for dry weight, total lipid, phospholipid (lipid phosphorus × 25), total and free cholesterol, cholesterol ester (combined cholesterol × 1.73), and neutral fat (calculated by difference). Dry weight is expressed as a percentage of wet weight and all lipid fractions are given as percentages of dry weight. Comparison with values given

TABLE 2.—*Liver Lipids of Dogs Fed Cholesterol and Thiouracil with and without Excess Dietary Choline*

Dog No.	Serum Cholest. Average	Arterio-sclerosis	Dry Wt.	Total Lipid	Phospho-lipid	Cholesterol			Neutral Fat
						Total	Free	Esters	
2.5% Choline Added to Diet									
	Mg. %		%*	%†	%†	%†	%†	%†	%†
33	970	+	30.0	12.4	4.8	1.0	0.6	0.7	6.3
34	1310	++	32.2	23.8	8.6	3.8	1.2	4.5	9.5
35	990	±	30.0	14.7	5.3	1.4	0.7	1.2	7.5
36	870	+	30.3	24.7	8.1	4.9	1.0	6.8	8.8
37	1250	++	29.8	20.0	4.6	4.7	1.0	6.4	8.0
38	1670	+++	27.0	22.9	9.3	3.7	1.1	4.5	8.0
Average	1177		29.8	19.75	6.78	3.25	0.93	4.02	8.02
No Choline Added to Diet									
40	840	+	26.3	17.9	6.9	2.4	1.2	2.1	7.7
41	704	+	30.7	21.2	9.0	2.4	1.0	2.4	8.8
42	1510	+++	29.4	14.3	5.2	3.1	1.1	3.4	4.6
43	950	+	24.5	23.7	9.6	2.7	1.1	2.7	10.3
Average	1001		27.7	19.3	7.68	2.65	1.1	2.65	7.85
Normal Dogs[16]									
				17.18	9.19	0.43	0.12	0.95	6.90

* Expressed as per cent of wet weight of liver.
† Expressed as per cent of dry weight of liver.

by Williams and associates[16] for normal dog livers shows that the cholesterol-thiouracil regimen for four months resulted in a marked increase in the cholesterol and cholesterol ester content of the livers. Two of the dogs receiving choline showed a lower liver cholesterol content than any of the 4 control dog livers analyzed. However, since the livers of the other 4 dogs fed choline contained more cholesterol than any of the controls, this difference cannot be ascribed to the presence of the added choline in the diet.

The basic diet used in these experiments was adequate in choline as well as in all other factors required for normal growth and reproduction. In this respect it resembled the normal diet of adequately nourished human beings. It is possible that choline may play some role in the metabolism of cholesterol as well as in the metabolism of other lipids, but apparently the choline content of the basic diet is sufficient to exert a maximal effect.

Summary

It was not possible to demonstrate that choline had any effect upon 9 dogs on an arteriosclerosis-producing regimen of cholesterol and thiouracil feeding. Dogs receiving the largest amount of choline that they could tolerate did not differ from control dogs in the serum level of cholesterol or phospholipids, in the degree of fatty infiltration of the liver nor in the extent and severity of the arterial lesions.

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White Thromboembolism in the Hamster Cheek Pouch after Trauma, Infection and Neoplasia

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White thrombosis and embolism were investigated by cinephotomicroscopy in the transillumined cheek pouch of the hamster in an experimental study of factors which may be involved in the febrile hemolytic syndrome in man, characterized by a finding of generalized platelet thrombosis of arterioles, capillaries and veins at autopsy. Endothelial trauma resulting from vascular occlusion produced platelet thrombosis and embolism. Dicumarol prevented the formation of platelet thrombosis and embolism after trauma. Heparin produced spontaneous platelet emboli and both heparin and dicumarol resulted in a leukocytic thrombosis. Platelet and leukocytic coatings and embolization were photographed during staphylococcus infection and malignant neoplasia. Sludged blood was not found in trauma, infection or malignant neoplasia.

AN EXPERIMENTAL investigation of the production of intravascular agglutination and the factors involved is significant because of the frequency of thromboembolism, both spontaneous and postoperative, and the practice of administering the anticoagulants heparin and dicumarol as therapeutic agents. In recent years, the intravascular agglutination of circulating erythrocytes bound together by a sticky glassy precipitate to form "sludged blood" has been reported by Knisely and co-workers.[1–5] These workers [1, 3] described the formation of sludged blood in traumatic areas and proposed that sludged blood may form thrombi in the capillaries, resulting in the production of traumatic shock. Laufman, Martin and Tanturi[6] occluded the mesenteric vein in the dog and reported that heparin and dicumarol caused a diminished adherence of erythrocytes to the vessel wall but did not prevent the formation of sludged blood. The authors concluded that anticoagulants prevent thrombosis by preventing agglutinated erythrocytes from adhering to the endothelial wall. Laufman, Martin and Tuell,[7] using Knisely's quartz rod apparatus with magnifications of × 25 and × 48, found a clumping of blood elements which they interpreted to be the blood sludge described by Knisely. Odell, Aragon and Pottinger,[8] using Knisely's technic for observing, at × 48, the blood flow in the conjunctiva of man, found sludged blood in a small group of pathologic cases and in pregnancy. Timonen and Zilliacus[9] reported sludged blood in patients with skin allergies. Bloch[10] reported sludged blood of the "soft clump" type in the conjunctivas of 262 patients suffering from poliomyelitis.

Except for a single in vitro experiment[1] in monkey malaria, erythrocyte masses have not been probed or otherwise tested for adhesiveness. Blood flow examined under the usual binocular magnifications frequently shows that the erythrocytes are arranged in groups simulating the condition referred to as "sludged blood." This may account for the widespread occurrence of sludge reported in the literature under conditions where it would hardly be expected. For example, Fowler[11] described "blood sludge" in the small venous vessels of the conjunctiva of the cat on electrical stimulation of the cervical sympathetic nerve and after injections of epinephrine. Since the procedures of Fowler produced vasoconstriction, sometimes rhythmic, the observations of Fahraeus[12] that contractions of blood vessels may cause the appearance of aggregated clumps of erythrocytes in the blood stream provide a physiologic explanation.

The importance of white thrombi, especially the intravascular agglutination of blood platelets, is not recognized generally, although 20

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or more fatal cases have been reported[13–25] in the last 25 years, characterized by febrile hemolytic anemia, thrombocytopenia, and marked generalized platelet thrombosis of arterioles, capillaries and veins. Zucker[26] reported platelet thrombi limited to the openings cut in the walls of the rat mesenteric blood vessels. Smith and co-workers[27] observed the presence of a white coating, probably platelets, on the walls of blood vessels in the wing of the bat after x-irradiation. Youngner and Algire,[28] and Algire and Schlegel[29] found circulating white emboli (not identified as platelets) in the blood vessels in a transparent skin flap preparation in the mouse. Copley and Robb[30, 31] found that heparin did not prevent the clumping of platelets in vitro in the dog and mouse. Copley[32] demonstrated, in vivo, the presence of circulating platelet emboli of leukocytic size in the cheek pouch of the hamster following the administration of heparin. Copley[33] and Fleck[34] have speculated that hyperheparinemia, producing platelet agglutination, may be an important factor in the production of various types of shock. Furthermore, Copley[33] suggested that heparin and platelet agglutination may account for the thrombocytopenia and hemorrhagic events of radiation sickness. However, nowhere in the literature has fragmentation of platelet thrombi to form circulating emboli been reported in connection with anticoagulant administration. Neither has the method of resolution of platelet thrombi been described.

During the past 15 years, we have been investigating vascular phenomena by direct microscopic observation and motion picture recording of the blood flow in the transillumined retrolingual membrane of the frog, *Rana pipiens*,[35] and the cheek pouch of the hamster, *Mesocricetus auratus*.[36, 37] In view of the controversial significance of "sludged blood" and the need for more direct microscopic investigations on thrombosis and embolism, we have investigated[38, 39] the characteristics of blood flow under pathologic and traumatic conditions similar to those in which sludge has been reported.

Methods

Hamsters were anesthetized with urethane administered intraperitoneally (0.15 Gm. per 100 Gm. body weight) or with intraperitoneal injections of Nembutal (0.15 cc. pentobarbital sodium per 100 Gm. body weight). At least one cheek pouch, and often both, were transillumined in 75 hamsters by the method described previously for investigation of the peripheral vascular neuromotor mechanism.[37, 40] The anesthetized hamster was placed in a spun stainless steel operating dish and the cheek pouch was everted over an optical glass transilluminating block, covered with Ringer's solution, and maintained at 37 C. during observations by means of a thermostatically controlled electrically heated microscope stage. In the frog with brain and medulla pithed, the retrolingual membrane was prepared and transillumined as described previously.[41] Simultaneous observations and motion picture records were made by means of a light-splitting prism mounted on the body tube of the microscope in place of the three way nosepiece.*

Our methods for transilluminating the cheek pouch of the hamster and the retrolingual membrane of the frog permit clear visualization and photography of the characteristics of blood flow, the nature of the intravascular elements, and the structural components of the blood vessel wall. Microscopic magnifications varying from × 200 to × 1200 have been used. The methods used by other investigators for observing sludged blood in man, and in animals for the most part, have been limited by the necessity of examination by reflected illumination and relatively low magnifications (× 54, × 90). Furthermore, we have tested erythrocyte groups by compressing the blood vessel with a microprobe as an indication of intravascular agglutination.[38]

The pathologic and traumatic conditions selected for investigation were of three principal types: first, physical and chemical injury; second, infection; and third, malignant neoplasm. These conditions correspond with the various circumstances under which Knisely, Block, Eliot and Warner[3] reported the presence of sludged blood. The sixty or more diseases in which sludged blood has been reported may be classified similarly.

Physical injuries were produced in 24 hamsters and numerous frogs by occlusion of the main blood vessels of the transparent membranes with small rubber-tipped serrefines or with hemostatic forceps for a time interval of 20 to 45 minutes. Slight physical injuries were made by burning small areas in the membranes with a hot needle, by probing the small blood vessel with a microneedle, and by injurious faradic stimulation with a microelectrode.

* Staro Instrument Company, Cambridge, Mass.

Limited chemical trauma was produced by the topical application of croton oil and mustard oil from a micropipet. Extensive trauma resulted from massive limb crushing, visceral manipulation, and a combination of both procedures.

Direct microscopic observations of intravascular conditions have been made in 11 dicumarolized hamsters (1.25 mg. suspended in gum acacia per 100 Gm. body weight administered by stomach tube daily from one to five days) and in 4 heparinized hamsters (1.5 mg. per 100 Gm. body weight injected into the femoral vein) with and without vascular occlusion. Blood platelet counts were determined in anesthetized and also unanesthetized hamsters from cardiac blood by a modification of the Nygaard method. A sample of 0.1 cc. of cardiac blood was drawn into a 1 cc. tuberculin syringe containing 0.9 cc. of sodium oxalate (1.1 per cent) and a minute amount of brilliant cresyl blue. Erythrocyte sedimentation was permitted for one hour in a paraffin-lined serologic tube containing 1 cc. of sodium oxalate. Counts were made by means of a Spencer Bright Line Haemacytometer from a sample of the supernatant fluid taken just above the erythrocyte sedimentation line by means of a red cell pipet.

For the investigation of peripheral blood flow during infection, 18 hamsters were inoculated intraperitoneally with *Staphylococcus aureus* (beta hemolytic). The inoculations consisted of 0.4 cc. bacterial suspensions prepared by adding 10 cc. of 0.5 per cent sterile sodium chloride to 24 and 48 hour agar culture slants. Hamsters were selected for blood vessel microscopy at 24 hour intervals over a period of five days after inoculation. Blood counts (red cell, total and differential white cell, and platelet) were made at daily intervals for seven days. Bacteriologic cultures were prepared from blood and peritoneal fluid. The characteristics of blood flow were investigated also in frogs with the infectious disease known as "red leg."

The characteristics of blood flow associated with malignant neoplasms were studied both by reflected light and by transillumination in the cheek pouches of 160 hamsters with advanced sarcomas of carcinogenic origin and with cheek pouch transplants of carcinogen-induced sarcomas.[42] Hematologic studies, including platelet counts, were made on 13 of these animals.

Results and Implications

Platelet Thrombosis and Embolism Resulting from Trauma

Traumatic injury of the vascular endothelium and complete stasis in the blood vessels of the cheek pouch were produced by complete occlusion of the supplying arteries and veins for a period varying from 20 to 45 minutes. After release, the blood flow resumed slowly during the next several minutes. Recovery from stasis occurred first in the venules by the formation of anastomosing intravascular pathways within the masses of static erythrocytes until the channels coalesced to fill the lumen of the vessel. Within the next 10 to 15 minutes translucent granular aggregates were found adhering to the walls of numerous venules, particularly at vascular junctions but also at points remote from junctions. Each white aggregate increased in size, forming a thrombus which frequently filled the lumen and blocked completely the blood flow in the venule. Such thrombi were observed in venules varying in size from 10 to 200 microns in diameter. As a result the venous blood leaving the capillary network was rerouted through adjacent unthrombosed venules, resulting in reversals in the direction of blood flow in the capillary network. Under high magnifications, the white thrombi proved to be acellular. In a number of cases a portion of a venule containing a thrombus was excised by means of a microknife and the intravascular elements were suspended in the diluting fluid of Rees and Ecker[43] and stained with brilliant cresyl blue. Leukocytes, erythrocytes and fibrin could not be demonstrated in the thrombus. The primary component of the thrombus was identified as the blood platelet.

Blood platelet thrombi frequently occluded venules completely, producing stasis in the corresponding capillary network for variable and indefinite periods. The platelets comprising a a thrombus were strongly adherent to each other and to the vessel wall, as determined by probing with a microneedle mounted in a micromanipulator. However, circulating erythrocytes were observed cutting a maze of anastomosing channels which coalesced, undermined the platelet mass and set free emboli varying in size and shape. Platelet thrombosis and embolus formation have been observed consistently after release from vascular occlusion (figs. 1*A*, *B*, *C* and *D;* 2*C*, *D* and *E*). Some emboli were smaller than the hamster erythrocyte (7.0 microns) and others were large enough

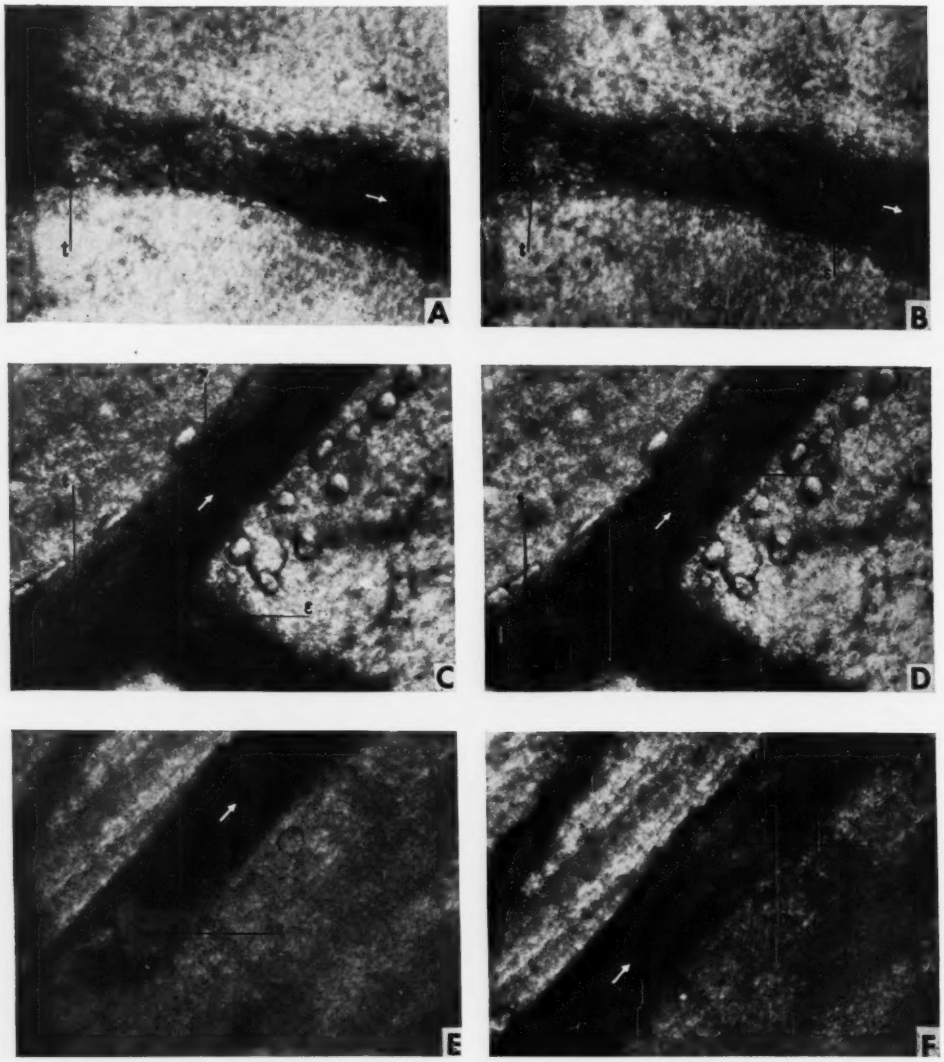

FIG. 1. Enlargements from cinephotomicrographic sequences showing thrombosis and embolism in cheek pouch of hamster following release from vascular occlusion. Magnification × 100. *A* and *B*. Blood platelet thrombus (*t*) in a venule (88 microns in diameter). In *B*, circulating platelet embolus (*e*) formed by fragmentation of the thrombus. *C* and *D*. Fragmentation of a platelet thrombus (*t*) in a venule (90 microns in diameter) of the cheek pouch opposite to that occluded. Individual platelets (*p*) were swept from the thrombus to join the embolus shown turning the corner at the vascular junction. *E* and *F*. Movement of a large platelet embolus (*e*) in a venule (100 microns in diameter). Progression is shown in *F* taken 1.5 seconds after E.

to contact opposite walls of blood vessels 50 to 100 microns in diameter (figs. 1*E* and *F*). At times vast numbers of platelets were swept off a thrombus individually, like "drifting snow," into the circulating stream (fig. 1*C* and *D*). Platelet emboli resulting from vascular occlusion have been detected and photographed in the arterioles of the occluded cheek pouch

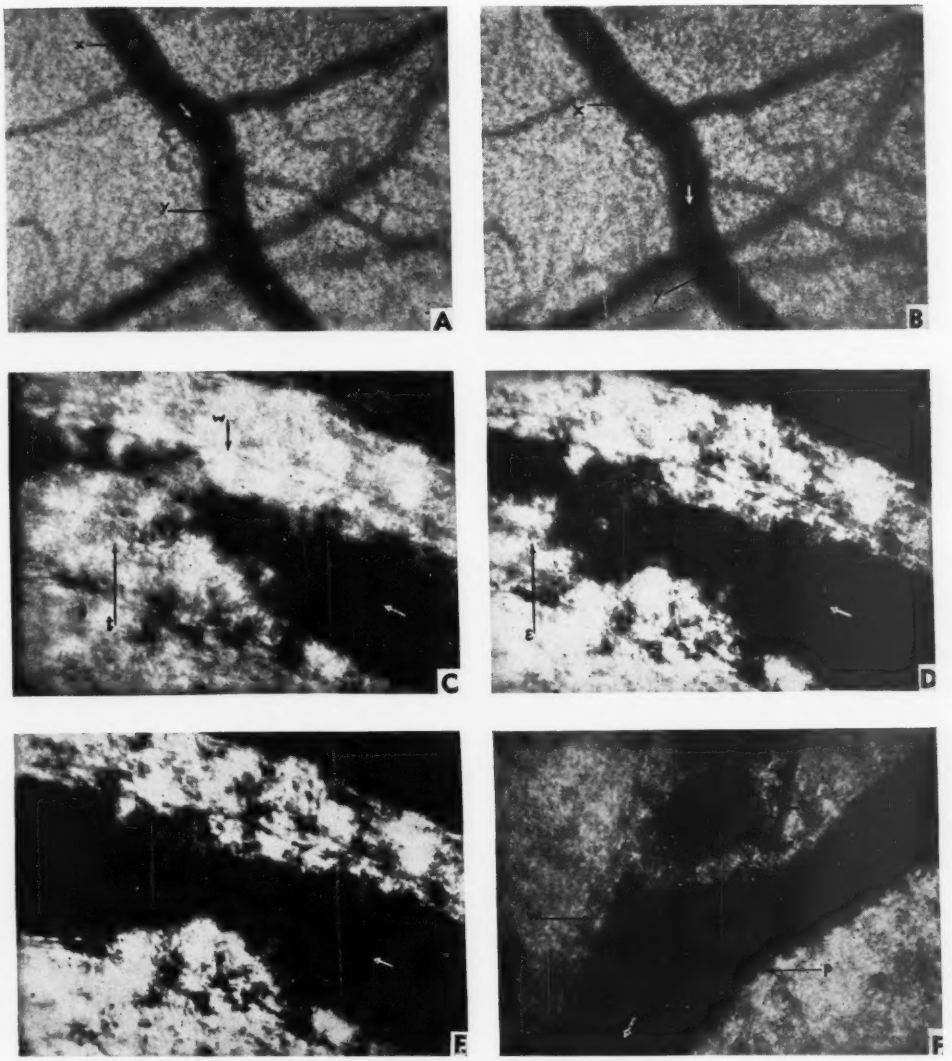

FIG. 2. *A–E*. Enlargements from cinephotomicrographic sequences taken after occlusion. *A*, circulating platelet emboli at *x* and *y* in an arteriole (34 microns in diameter), photographed at 64 frames per second. *B*, taken one-sixteenth of a second after *A*, shows progression of emboli. Magnification × 100. *C*, *D* and *E*. Successive stages in the formation of an embolus. Platelet thrombus (*t*) almost stops the blood flow in a venule (67 microns in diameter) in *C*. In *D*, fragmentation of the thrombus forms an embolus (*ε*) which is carried away in *E*. The vessel wall (*w*) opposite the thrombus is coated heavily with platelets. Magnification × 520. *F*. Infection with *Staph. aureus*. Mixed thrombus composed of platelets, leukocytes and trapped erythrocytes at a venous junction (vessel diameters 72, 86 and 101 microns). Note platelet coating (*p*). Magnification × 260.

(fig. 2*A* and *B*) and also in the blood vessels of the opposite unoccluded pouch (fig. 1*C* and *D*). Consequently, unresolved platelet masses must enter the heart, lungs, and other vital organs. Many large platelet emboli traverse the vascular pattern of the cheek pouch, and presumably that of other organs without forming thrombi, undoubtedly because of the presence

of arteriovenous anastomoses. We have frequently followed emboli shunting across from the arterial side. This is direct evidence for the phenomenon demonstrated indirectly by Prinzmetal and co-workers[44] using glass beads of various diameters.

Platelet thrombi and emboli were produced at will by slight endothelial injury caused by inserting the point of a microneedle obliquely through the vessel wall, abrading the lining, and then withdrawing the needle. A platelet thrombus was immediately formed, seemingly platelet by platelet, partially occluding the vessel until it was swept away as an embolus. Local injury was also produced by the topical application from a micropipette of a minute amount of desoxycorticosterone glucoside (Percorten, Ciba) used in a nonphysiologic concentration. Platelets and white cells accumulated temporarily at the point of application. The conditions of blood flow were examined in the cheek pouches of hamsters during severe trauma produced by massive limb crushing, visceral manipulation and a combination of both procedures. In these drastic experiments emboli in the cheek pouch vessels were few. The reason for this is not known. However, because of the severity of the injury, blood flow through the damaged tissues was probably negligible. How efficient the liver may be in removing agglutinated platelets from portal blood is not known to us.

Platelet counts were made on cardiac blood both before and after vascular occlusion, using an appropriate modification of the Nygaard method. The normal values for the cellular components of hamster blood have been reported by Stewart and co-workers,[45] but not for blood platelets. We have found no record in the literature of platelet determinations in the hamster. In the normal hamster (anesthetized and unanesthetized) the count ranged from 420,000 to 460,000 per cu. mm. of blood in 5 animals. Determinations made during platelet thrombus formation did not vary significantly.

In the mesentery of the frog, intravenous platelet thrombi were observed after vascular occlusion of the large mesenteric vessels. However, embolus formation comparable to that of the hamster was not seen. Microinjuries were produced on the walls of small blood vessels in the retrolingual membrane by probing with a microneedle, stimulating with an injurious faradic current by means of a microelectrode, and by applying topically croton oil and mustard oil from a micropipet. Leukocytes accumulated at the injured portion of the blood vessel and persisted only for several seconds to several minutes after the stimulus was discontinued. Slight local injuries did not produce thrombus formation or stasis. Small droplets of croton oil deposited on the epithelium of the retrolingual membrane were surrounded by groups of ciliated squamous epithelial cells and carried away. Minute droplets of croton oil and mustard oil (5 to 15 microns in diameter) applied to the epithelial surface directly above small arterioles produced marked vasodilation resulting from stimulation of the perivascular nerve plexus, since vascular segments not exposed to contact with the irritants were involved. Vasodilation persisted during the period of exposure to the irritant. Prolonged exposure was characterized by the adherence of white cells to blood vessel walls in the exposed area and ultimately by the development of stasis.

The extensive platelet thrombosis and embolism resulting from vascular occlusion in the hamster has significant surgical implications and suggests that blood platelets may be more important than previously recognized in the etiology of thrombosis.

The Effect of Dicumarol and Heparin

The effectiveness of dicumarol in the prevention of platelet thrombi and embolism resulting from vascular occlusion was investigated by direct microscopy. Cheek pouches were everted for transillumination on the first, second, third, fourth and fifth days following administration daily of 1.25 mg. of dicumarol by intubation. Normally, relatively large blood vessels may be severed with practically no bleeding during the minor surgery involved in preparing the cheek pouch. After dicumarolization, preparation of the cheek pouch resulted in considerable bleeding and a greatly prolonged clotting time. In several animals

petechiae formed. Portions of certain arterioles were constricted markedly, alternating with dilated sections, thus forming sausage-shaped vascular segments filled with erythrocytes. Considerable hemoconcentration was noted, probably due to an increase in permeability, but stasis did not predominate. Spontaneous platelet emboli and thrombi were not seen.

Blood platelet counts made at intervals between 24 to 96 hours after administration of dicumarol were 50 per cent greater than the normal count. The reason for the increase is not known. Several factors which may possibly be involved are as follows: first, a decreased adhesiveness of platelets to each other and to erythrocytes so that fewer platelets were carried down by sedimenting red cells in the counting technic; second, an increased production of platelets; third, a decreased destruction and removal of platelets; and fourth, an increased mobilization of platelets from possible storage depots.

Trauma was produced in the cheek pouch of dicumarolized hamsters by vascular occlusion for 20 to 45 minutes. The blood vessels were released from occlusion and examined at × 260 and × 520 for the presence of platelet thrombi and emboli. No platelet thrombi and no platelet emboli were found, except for small emboli in 1 hamster five days after administration of a single dose. Consequently, dicumarol prevented the formation of platelet thrombosis and embolism after trauma. This is direct microscopic evidence to support the contention of clinicians that dicumarol is of therapeutic value in preventing the propagation of a thrombus and in decreasing the recurrence of coronary thrombosis.[46–50]

Irrespective of vascular occlusion, vast numbers of leukocytes were observed consistently after 24 to 48 hours coating the walls of venules and capillaries in dicumarolized hamsters. This might conceivably impair the oxygen, carbon dioxide and nutrient transfers in vital tissues and organs. It must increase the peripheral resistance. Aggregates of white cells were observed breaking away from the vascular endothelium to form leukocytic emboli which subsequently lodged at vascular junctions to form thrombi blocking the blood flow. This phenomen may be of possible significance in cases where controlled dicumarol administration has been implicated in fatalities.[51] No reference to the tendency of dicumarol to cause plating of leukocytes on the lining of small blood vessels has been found in the literature. It may be important to screen anticoagulants for leukocyte aggregating properties. We are investigating the characteristics of other anticoagulants.

The effectiveness of heparin in the prevention of platelet thrombosis and embolism was also investigated. The cheek pouch was everted for transillumination within 30 minutes after the administration of heparin. Preparation of the cheek pouch in heparinized hamsters resulted in excessive bleeding and prolonged clotting time. From the moment of initial observation, spontaneous platelet emboli were seen moving in the vessels of the cheek pouch. This confirms the report by Copley[32] that heparin administration in the hamster produced circulating platelet emboli. The size of the emboli varied from that of a leukocyte (upper limit reported by Copley) to a mass 20 microns or more in diameter.

In view of the fact that heparin produced platelet emboli spontaneously, only a few vascular occlusion experiments were attempted, and the results of these were inconclusive. Presumably the platelets were agglutinated by heparinization and unavailable for agglutination following trauma by vascular occlusion. In heparinized hamsters leukocytes were observed consistently coating the walls of small blood vessels, even forming attached clumps, but no leukocytic emboli were seen. This confirms, in original, physiologically mature blood vessels, the increased adhesiveness of leukocytes and the absence of leukocytic emboli reported by Essex and Graña[52] in the newly formed regenerated blood vessels in transparent chambers inserted in the ears of rabbits.

Experiments are in progress to determine nontoxic substances which will prevent the formation of platelet and leukocytic thrombi. The anticoagulants heparin and dicumarol do not appear to be promising therapeutic substances in this respect, because, *per se*, they cause leukocytes to adhere to the vascular endothe-

lium, namely leukocytic thrombosis, and in addition dicumarol produces leukocytic emboli.

Platelet and Leukocytic Coating on the Vascular Endothelium, and Embolism During Infection

The endothelial lining of venules, capillaries and many small arterioles in the cheek pouch was coated with a continuous layer of platelets and leukocytes varying in thickness. This was observed from 24 to 120 hours after intraperitoneal inoculation with a suspension of *Staphylococcus aureus*. In the smallest vessels the leukocytes adhered to the endothelium and did not roll along the vessel wall in the usual way. Frequently the blood stream in a vessel 20 to 30 microns in diameter was confined to a tortuous channel sufficient only for the passage of erythrocytes in single file. The leukocytic coating was greatest 24 to 48 hours after inoculation, but persisted during the course of the infection. Septicemia was demonstrated by the preparation of positive cultures of the original organism from cardiac blood obtained 24, 48, 96 and 120 hours after injection. Phagocytized bacteria were found within leukocytes in blood smears made from infected hamsters. Several hamsters died within 96 hours after inoculation, but the majority recovered. The intimal endothelium of the blood vessels in the cheek pouches of hamsters which recovered was normal.

Numerous venules were lined by a white adhesive coating (fig. 3*A* and *B*). Commonly white emboli were seen (fig. 3*B*). Smear preparations of the coatings were made and blood platelets, leukocytes and erythrocytes were demonstrated, but no fibrin was seen. The erythrocytes were trapped by platelet aggregations. Mixed thrombi were seen also at venous junctions, completely blocking the circulation in one venule (fig. 2*F*).

In staphylococcus infected hamsters, large white emboli composed predominantly of clumped leukocytes were seen in the blood vessels of the cheek pouch. We have observed the formation of leukocytic emboli from the coating on the vascular endothelium. Occasionally we have followed successfully the course traversed by a white cell embolus and have observed it entering a precapillary arteriole by stretching longitudinally and "worming" through the lumen to lodge at a capillary junction and form a thrombus unresolved during the period of observation.

The appearance of mixed platelet-leukocytic thrombi and emboli in animals with *Staph. aureus* infection is accompanied by a thrombopenia and leukocytosis. The platelet count in cardiac blood decreased in all cases and dropped as low as 27,000 and 30,000 at 48 and 72 hours respectively. The differential white cell count varied between the following limits during the course of the infection: 60 to 86 per cent polymorphonuclear leukocytes, 6 to 32 per cent lymphocytes, and 6 to 19 per cent monocytes. This is in sharp contrast with normal values, as reported by Stewart and co-workers[45] and confirmed by us, of 32 to 35 per cent polymorphonuclear leukocytes, 63 to 66 per cent lymphocytes and 1 to 2 per cent monocytes.

The characteristics of blood flow were investigated also in the retrolingual membranes and the mesenteries of many frogs with the infectious disease known as "red leg." The preparations were characterized by an increase in leukocytes in the small blood vessels. However, emboli and the extensive leukocytic coating comparable to that found in the hamster were not observed in the frog. The vascular pattern in the retrolingual membranes of frogs with "red leg" appeared to be in a state of flux. Vasodilation predominated and considerable stasis was found. Some capillaries appeared to be degenerating, and in other parts of the field capillary endothelial sprouts were seen. Portions of the capillary network consisted of unusually small and atypical complex anastomoses.

The discovery of platelet and leukocytic aggregates in the vascular system of hamsters during infection may be highly significant. The mechanism involved in the formation of the aggregations has not been determined. Considerable controversy exists concerning the possible role of blood platelets in the removal of bacteria from circulating blood. Houlihan and Copley[53] have demonstrated in vitro an increased adhesiveness of platelets and a marked clumping when rabbit blood was

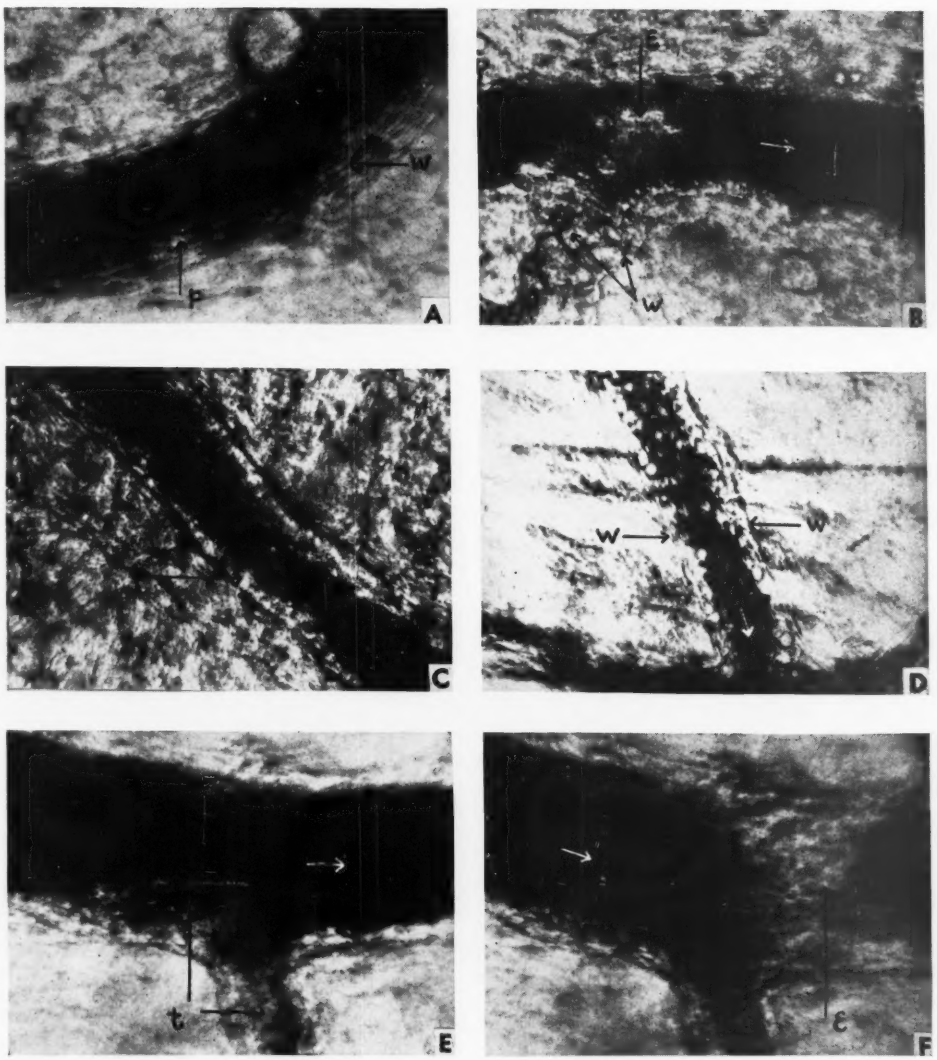

FIG. 3. *A, B.* Enlargements from cinephotomicrographic sequences in *Staph. aureus* infection. *A,* blood platelets and leukocytes coating the endothelium of a venule (70 microns in diameter). *B,* an embolus (*e*) shown in a venule. Walls (*w*) of adjoining venule completely occluded by platelets. *C–F.* From animals bearing an advanced methylcholanthrene tumor transplant in the other cheek pouch. *C,* heavy coating of platelets (*p*) lining a venule. *D,* leukocytic and platelet coating in a venule with walls (*w*) 35 microns apart. *E,* large thrombus (*t*) shown forming in a venule with extensive platelet coating. *F,* thrombus formed in *E* soon becomes an embolus (*e*). Platelet plug in smaller vessel remains. Magnification × 260.

mixed with *Staph. aureus* and other bacteria. The possibility exists that platelet and leukocytic masses may line the small blood vessels in various vital organs, including the brain, heart and lungs during severe infections. Such coatings on the endothelium might conceivably decrease the effective oxygen, carbon dioxide, and nutrient exchange between blood and

tissue fluids. The effect of larger thrombi incompletely or completely blocking the small blood vessels would be severe. Aggregates of this type might well explain the central nervous system manifestations and mental confusions which frequently accompany severe infection. The symptoms associated with many infectious diseases are often more severe than would be expected in consideration of the known characteristics of the infecting agent. Furthermore, an analysis of the case histories of the twenty or more sudden deaths characterized by autopsy findings of extensive generalized platelet thrombosis of arterioles, capillaries and venules[13–25] indicates a correlation between infection and platelet thrombosis.

White Thrombosis, Embolism and Leukocytosis Associated with Malignant Neoplasia

Large circulating white emboli were seen routinely by reflected light (× 15) in the cheek pouch vessels of nearly all hamsters (150) with advanced sarcomas induced by methylcholanthrene, and with large advanced transplants (2 to 3 cc.) of methylcholanthrene-induced sarcoma in the opposite cheek pouch. When the blood flow in 14 of these hamsters was examined by transillumination at × 260 and × 520, the walls of venules, capillaries and many arterioles were seen to be lined with immobilized leukocytes and platelets (fig. 3*D*). In many areas a coating of these elements nearly occluded the lumen for a considerable length (fig. 3*C*). At certain points thrombi were alternately forming and breaking away, producing emboli of various sizes (fig. 3*E*, *F*). Microscopic examination of blood smears showed many of these emboli to be composed of blood platelets. Leukocytic emboli were also found, in some cases large enough completely to plug small vessels.

The tumor bearing hamsters were asthenic and anemic, as indicated by pallor of the nose and extremities. The blood stream was translucent, further suggesting a severe anemia. Red cell counts were made on 12 hamsters with cheek pouch tumor transplants 60 to 108 days old. One additional hamster was used with a transplant 22 days old. The red cell counts varied from 4.6 to 10.8 million. The extremes were represented by one case each. The other counts fell within the accepted normal values for this age group. The anemic appearance was therefore not due to erythrocyte deficiency, but presumably to lowered hemoglobin. In all cases except one there was a definite leukocytosis, and in 8 cases the normal ratio of polymorphonuclear leukocytes to lymphocytes was reversed, as in hamsters infected with *Staph. aureus*. In 6 cases with extreme leukocytosis (23,200 to 35,500 per cu. mm.) the ratio varied from 63 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes to 93 per cent and 3 per cent, respectively. In all cases there was an increase in monocytes. In 11 cases the monocytes constituted 5 per cent to 21 per cent. The blood platelet count varied from a low of 97,000 to a high of 1,255,000 per cu. mm. Two cases were below and 5 above the normal range, which is between four and five hundred thousand. The variability in the white elements of the blood may be due to the heterogeneity of the group so far as the ages of the transplants were concerned. In some cases ulceration of the tumor and secondary infection were apparent. In other cases very extensive white coatings and numerous white emboli and plugs were observed. Further work is in progress in this laboratory on the properties of the blood in hamsters with advanced tumors of carcinogenic origin.

Absence of Sludged Blood in Trauma, Infection and Malignant Neoplasia

We have studied the characteristics of blood flow in transillumined membranes under high magnification for the possible formation of sludged blood under pathologic and traumatic conditions. Sludged blood was reported originally by Knisely[2] in monkeys in the terminal stages of malaria and described as an agglutination of erythrocytes forming circulating "rafts" held together by means of a glassy precipitate as determined by microprobing in vitro. These erythrocyte emboli were seen lodging at the capillary junctions to block the blood flow. The presence of sludged blood, reported by Knisely and co-workers,[3] was de-

termined in man under conditions which did not permit clear visualization and adequate testing for the presence of a sticky coat binding erythrocytes together. In hamsters we have simulated experimentally the general conditions in which sludged blood has been reported in man. We find that erythrocytes have a tendency to circulate at times in groups separated by plasma, platelets and leukocytes, due to vasomotor rhythmicity and consequent plasma skimming. This is undoubtedly the phenomenon described by Fowler[11] after stimulation of vasoconstrictor nerves and intravascular injection of vasoconstrictor substances and reported as sludged blood. We think that Knisely has extended his concept, without crucial evidence, to include blood flow characteristics which differ from those of the sludged blood he originally defined.

In several clinical laboratories, the classic rouleau formation of Fahraeus has been confused with the concept of sludged blood.[4, 6–10] Hirschboeck and Woo[54] and Robertson, Wolf, and Wolff[55] report that the conjunctival intravascular phenomena referred to as sludged blood occur in both normal and diseased states and are of no great clinical significance. The term "sludged blood" is obviously a misnomer in the majority of circumstances in which it has been used. We have microprobed, in vivo, erythrocytes circulating in groups, and find no evidence for sludge in the original sense of the term. Furthermore, erythrocytes in stasis for long periods (one to five days) remained unagglutinated and free to move individually when the vessel wall was compressed with a microneedle.

Although Knisely[3] has reported sludged blood in frogs, we have not seen it in the retrolingual membrane, web, lungs, bladder, mesentery or vocal sac, even in conditions of severe trauma produced by burning or physical injury. We find no sludged blood in the blood vessels of the cheek pouches of hamsters with staphylococcus infection, malignant neoplasia, and trauma including massive limb crushing, visceral manipulation, a combination of both procedures, and production of small burns in the pouch.

Summary

1. Platelet thrombosis and embolism were produced in the distal blood vessels of the transillumined cheek pouch of the hamster by trauma of the endothelium resulting from vascular occlusion, for 20 to 45 minutes, at the attached end of the pouch. Cinephotomicrographs were taken demonstrating the formation of platelet thrombi and emboli, especially at venous junctions, both in the same pouch and in the pouch opposite to that occluded. Thrombus fragmentation produced circulating platelet emboli, which were recorded in venules and arterioles.

2. Dicumarol prevented the formation of platelet thrombi and platelet emboli after vascular occlusion. However, without vascular occlusion, dicumarol produced both leukocytic thrombosis and embolism.

3. Heparin produced platelet emboli, *per se*, but no platelet thrombi were found. However, a leukocytic coating (thrombosis) was produced by heparin, but no leukocytic emboli were seen.

4. Infection with *Staph. aureus* produced mixed platelet and leukocytic coatings and emboli of similar nature, accompanied by thrombopenia and leukocytosis. The correlation between infection in man and white thromboembolism is considered.

5. In malignant neoplasia (cheek pouch transplants of methylcholanthrene-induced sarcoma) white emboli composed largely of platelets were found. Mixed platelet and leukocytic coatings, as well as leukocytosis were characteristic.

6. Sludged blood was not produced by trauma, infection, and malignant neoplasia.

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Beriberi Heart in Iowa Veterans

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Beriberi heart disease does not constitute a rigid syndrome because the severity of cardiac failure, associated peripheral neuritis, other concomitant signs and symptoms, and response to treatment are variable. Five patients with peripheral neuritis, edema and evidence of cardiac failure are presented. All improved after treatment, and, in two instances, there was marked reduction in cardiac size. Beriberi was thought to be the most likely diagnosis in each case, since there was no evidence of other etiology.

THIS communication deals with 5 cases of beriberi heart disease recognized at the Des Moines Veterans Hospital among 7,912 admissions between October, 1948 and January, 1950. None of these Iowa residents was a prisoner of the Japanese. Beriberi was considered a disease of the Orient until about 25 years ago. It has been regularly reported in the southern and eastern portion of the United States, but only once (to my knowledge)[1] in the "grain belt" regions.

All 5 cases conform for the most part to Blankenhorn's diagnostic criteria[2]: (1) enlarged heart with sinus rhythm; (2) dependent edema; (3) elevated venous pressure; (4) peripheral neuritis or pellagra; (5) nonspecific changes in the electrocardiogram; (6) no other cause evident; (7) gross deficiency of diet of three months or more; and (8) improvement and reduction of heart size after specific treatment or autopsy findings consistent with beriberi (see tables 1 and 2).

CASE REPORTS

Case 1. W. B., age 34, was admitted Oct. 23, 1948 with a three year history of taking 10 to 13 ounces of whiskey daily, eating very little and gradually losing 25 pounds of weight. Two months before entry he fell while walking and began to have weakness, exertional dyspnea, cough and calf pain. Ankle edema appeared three weeks before admission.

Examination revealed a hyperkinetic, perspiring, mildly dyspneic man. Temperature was 99 F., pulse 104, respirations 24, and blood pressure 120/70. The lungs were clear. The heart was enlarged 2 cm. beyond the left midclavicular line. The apex beat was forceful, and there was a faint pulmonic diastolic murmur. The liver was palpable 3 cm. below the right costal margin, and there was marked pitting edema of the lower extremities. There was definite weakness of the extremities with inability to rise from a squat. The knee and ankle jerks were absent and the calves were tender on pressure.

Laboratory findings (see table 3): The spinal fluid contained 52.5 mg. of protein per 100 cc. Liver function tests were indicative of hepatocellular damage. Basal metabolic rate was minus 4 per cent on October 28.

Chest roentgenograms revealed the cardiothoracic ratio to be 15.25:30 cm., with prominent hilar markings and blunting of the right costophrenic sinus. Electrocardiogram was normal. The arm to tongue circulation time on November 2 was 21 seconds (Macasol), and the venous pressure was 24 cm.

Hospital Course. He was given 2 cc. Salyrgan intramuscularly on admission. After six days on a low sodium diet (200 mg. per day), only a trace of ankle edema remained and his weight was constant. At this time administration of thiamine was begun in daily doses of 20 mg. intramuscularly and 20 mg. orally, in addition to administration of choline and other vitamins by mouth and a high protein diet. A neurologist confirmed the diagnosis of B deficiency neuritis, for which physiotherapy was given. The murmur was absent on the second day. Electrocardiogram on Dec. 17, 1948 showed that the previously inverted T wave in lead III was now upright. Clinical improvement continued until discharge on Dec. 17, 1948.

He was readmitted for nervousness on June 15, 1949. There was no evidence of cardiac decompensation. The blood pressure was 104/86, and the reflexes had returned. The cardiothoracic ratio was 12.7:30 cm. The electrocardiogram was normal. The liver had decreased in size, and there was no bromsulfalein retention.

Comment. This patient had a mild degree of cardiac enlargement and neuritis (mixed type), and probably a mild cirrhosis.

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Sponsored by the Veterans Administration with the approval of the Chief Medical Director. Statements and conclusions by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE 1.—*Pertinent Data on Five Cases of Beriberi with Cardiovascular Manifestations*

Case Initials Age Sex	Duration of Dietary Deficiency	Enlarged Heart	Venous Pressure	Edema	Electrocardiogram	Other Signs of Deficiency
Case 1 W. B. 34 M	3 yrs.	+	24 cm.*	+++	Inverted T_3	Polyneuritis, moderate
Case 2 R. S. 32 M	Mild—4 yrs. Severe—8 months	—	?	+++	Low voltage	Polyneuritis, severe. Scurvy
Case 3 J. S. 39 M	4 yrs.	+	Cervical veins distended	+++	Normal	Polyneuritis, mild
Case 4 D. W. 38 M	6 yrs.	+++	Cervical veins distended	++	Inverted T_1 and CF_4 Low Voltage	Polyneuritis, severe
Case 5 L. L. 32 M	2 yrs.	++	12 cm.†	++	T flat in all leads.	Polyneuritis, moderate. Korsakoff's psychosis.

* Third hospital day.
† Sixth hospital day.
+ Slight, ++ Moderate, +++ Marked.

TABLE 2.—*Response to Therapy in This Series*

Case, Initials, Age, Sex	Treatment	Loss of Edema	Decrease in Heart Size†	ECG Changes
Case 1 W. B. 34 M	Thiamine. NaCl 250 mg./day for 6 days. Mercuhydrin	6 days* (Not weighed on admission)	Clinical in 10 days, 2.5 cm. 8 months later.	T_3 upright in two months. Normal
Case 2 R. S. 32 M	Thiamine. High protein diet	8 days* (Not weighed for 2 months)	? (Bedside films)	Increased voltage‡. T remained diphasic after 6 months treatment
Case 3 J. S. 39 M	Thiamine. NaCl 2 Gm./day	6 days.* 17 lbs. from 4th to 10th day	Clinically in 20 days.	Not repeated (left against advice)
Case 4 D. W. 38 M	Thiamine. Mercuhydrin digitalis NaCl 2 Gm./day	4 days.* 20.5 lbs. in 8 days	5.5 cm. in 2 months	Inc. voltage. Normal in 3 months§
Case 5 L. L. 32 M	Thiamine. NaCl 2 Gm./day	2 days.* 36 lbs. in 7 days	4 cm. in 4 weeks	Normal in 3 weeks

* Disappearance of pitting edema.
† As determined by repeated teleroentgenograms, except in cases 2 and 3.
‡ Pneumoperitoneum given.
§ See comments on fig. 3.

TABLE 3.—*Pertinent Laboratory Data*

	R.B.C. millions per cu. mm.	Hb. Gm./ 100 cc.	E.S.R. Cutler	Bsf.	C.C.F. 24 hrs. / 48 hrs.	T.T.	Serum Proteins Total / Albumin / Globulin	Chol. / Chol. Esters
Case 1, W. B.								
10/23/49	4.85	14.0	9 mm./hr	—	—	—	—	—
10/28/49	—	—	—	22%	—	—	6.06 4.60 1.46	—
11/18/49	—	—	—	—	2+ / 4+	3.9	—	240 / 56
12/1/49	—	—	—	2%	—	4.8	—	164 / 66
Case 2, R. S.								
6/24/49	3.69	11.0	38 mm./hr	—	neg. / neg.	1.5	5.05 3.05 2.00	—
8/5/49	4.01	12.5	—	—	—	—	7.65 4.38 3.27	—
Case 3, J. S.								
6/24/49	3.40	11.5	24 mm./hr	—	—	—	—	—
6/27/49	—	—	—	8.8%	neg. / 2+	2.0	8.71 5.80 2.91	—
6/30/49	5.74	16.0	12 mm./hr	—	—	—	—	334 / 187
7/8/49	—	—	—	5.2%	—	—	—	—
Case 4, D. W.								
7/5/49	3.10	9.5	17 mm./hr					
7/8/49	4.65	14 Gm.		8.8%				216 / 150
Case 5, L. L.								
1/9/50	4.33	12.0	—	—	—	—	—	—
1/12/50	—	—	19 mm./hr	—	neg. / neg.	1.8	7.0 3.9 3.1	
1/13/50	6.09	16.0	18 mm./hr	—	—	—	—	—
1/23/50	—	—	19 mm./hr	12.4%	—	—	7.2 4.6 2.6	—
2/3/50	—	—	14 mm./hr	3.0%	—	—	—	— / 223 / 131
2/13/50	—	—	8 mm./hr	—	—	—	—	—

E. S. R. = Erythrocyte Sedimentation Rate.
Bsf. = Bromsulfalein retention at 45 minutes.
C. C. F. = Cephalin-Cholesterol Flocculation.
T. T. = Thymol Turbidity.
Chol. = Blood Cholesterol in mg./100 cc.

Case 2. R. S., age 39, a bartender, was admitted May 27, 1949. He had been drinking from 4 to 20 glasses of beer daily and eating poorly for four years. For eight months he had consumed one-half pint of whiskey, one-half bottle of wine, and thirty cans of beer daily, and had eaten little. Eighteen months before entry he noted weakness of the legs. Sudden syncope occurred six months before admission and

a productive cough appeared. For several weeks he had experienced nausea, diarrhea, back and leg pains, dyspnea, ankle edema and weakness. Abdominal soreness and "numbness" and petechiae on the legs and arms had been present for 10 days.

Examination revealed an apparently well nourished, irritable, sluggish, orthopneic man. The pulse was 120, temperature 101 F., respirations 28, and blood pressure 132/80. The pulse was weak. The heart sounds were muffled, but there was no enlargement or murmur. Moist rales were heard throughout both lungs. A tender liver extended 3 cm. below the right costal margin. There was a moderate amount of ascites and marked edema of the back, scrotum, thighs and legs. An abscess was present on the anterior chest, and there was an ecchymotic area 5 by 8 cm. on the left shoulder. Numerous hyperkeratotic hemorrhagic hair follicles were present on the arms and legs. The gait was dragging, and rising from a chair required great effort. The deep reflexes were absent.

There was a moderate anemia (see table 3), and the sedimentation rate was 38 mm. in one hour (Cutler). The platelet count was 270,000 per cu. mm. Hemolytic *Staphylococcus aureus* was cultured from the cutaneous abscess. Tubercle bacilli were found in sputum. The spinal fluid protein was 61.5 mg. per 100 cc. Roentgenograms of the chest revealed bilateral infiltrations of far-advanced pulmonary tuberculosis involving less than one-third of each lung field. The electrocardiogram was abnormal with low voltage (fig. 1).

Hospital Course. For 10 days he was dyspneic, weak, and febrile, and was given penicillin and a high calorie, high vitamin diet. After eight days the edema had disappeared and generalized muscular wasting and malnutrition were apparent. The neurologist found muscular tenderness, diminution of all types of sensation in the lower extremities, bilateral foot drop, and absent reflexes, and made the diagnosis of B deficiency neuritis. Gastric analysis showed 100 degrees of free hydrochloric acid.

After June 22, 1949 the patient was given 20 mg. of thiamine intramuscularly daily, large oral doses of vitamins B and C, and one blood transfusion. Two months after admission he had lost 27 pounds. Subsequent roentgenograms showed a normal heart, and no progression of the tuberculosis. Pneumoperitoneum was induced, and physical therapy was prescribed for the neuritis. There was a progressive gain in weight and strength after August, and by October he could shuffle to the bathroom. An electrocardiogram on November 22 was abnormal with diphasic T waves in leads I and CF_4, but there was increased voltage as compared with the previous tracing (see figure 1). He was transferred to a tuberculosis sanatorium on Nov. 22, 1949. Eleven months after admission residual polyneuritis was still present.

Comment. There is no evidence that this patient had cardiac enlargement and the venous pressure was unfortunately not measured. The history, however, together with an advanced degree of typical B deficiency neuritis, associated evidence of scurvy, electrocardiographic changes, edema, orthopnea, hepatic enlargement and response to therapy strongly supports a diagnosis of beriberi heart disease.

Case 3. J. S., age 32, a bartender, was admitted June 21, 1949. Alcoholic intake had been excessive

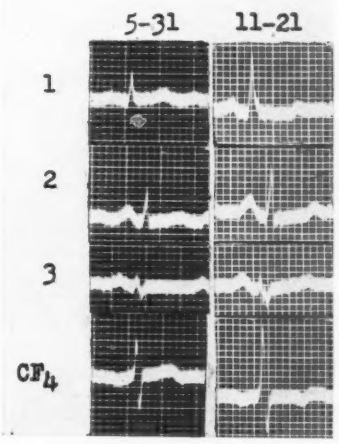

FIG. 1. Case 2. Electrocardiogram on fourth day showing low voltage. After six months there is increased voltage of QRS in leads I and II which may be due to pneumoperitoneum. The diphasic T waves in leads I and CF_4 are thought to represent residuals of beriberi.

for 15 years. For four years he had been inebriated nearly every day. He ate erratically. An episode of sudden syncope and cyanosis had occurred seven months before entry, followed by exertional dizziness, shortness of breath, cough, orthopnea, palpitation and ankle edema. For some time he had noted pains in the arms, legs and back, relieved by whiskey. Twelve days prior to admission edema began to increase rapidly.

Examination revealed a flushed, obese, tremorous, perspiring, and dyspneic man. Pulse rate was 110, respirations 22, and blood pressure 178/90. There was slight prominence of the eyes and the tongue showed marginal erythema. The neck veins were distended and rales were heard in the right lung base. The heart was enlarged 3 cm. beyond the left midclavicular line. Faint systolic apical and aortic

murmurs were noted. Moderate ascites was present, the liver was slightly enlarged, and there was marked edema of the lower extremities, thighs, and buttocks.

Laboratory findings (see table 3): Roentgenogram of the chest revealed a prominent left ventricle, with a cardiothoracic ratio of 16.5:32 cm. and clear lung fields. Electrocardiogram was normal.

Hospital Course. On a low sodium diet he lost twelve pounds from the fourth to the sixth day. At this time he complained of pain and numbness in the lower extremities. Deep muscular tenderness on pressure, particularly in the calves, and hypoactive to absent reflexes were then noted and administration of thiamine (20 mg. intramuscularly and 20 mg. orally) was begun. The murmurs disappeared on the second day.

Ten days after admission he was asymptomatic, ree of edema, and had lost seventeen pounds; the heart was normal in size, and carotid sinus irritability could not be demonstrated. On the last three days of his hospital stay blood pressure readings averaged 128/82, and the pulse ranged from 80 to 90. On the twenty-first day he left against advice. Letter follow-up six months later disclosed that he was still drinking, and had fatigue, anorexia and palpitation on exertion.

Case 4. D. W., age 38, laborer, was admitted July 1, 1949. He admitted alcoholism for six years. He ate three candy bars daily. His diet was meager, but only mildly deficient in thiamine. He had had episodes of syncope and faintness for five years. In 1943 and 1945 his blood pressure was slightly elevated. Eight months prior to admission exertional dizziness, dyspnea, and ankle edema began, and a heart murmur was noted. For six months he had numbness and pain in the feet and fingers and muscular soreness. Two months later palpitation and paroxysms of nocturnal dyspnea began. Dyspnea and ankle edema progressed in severity before admission.

Examination revealed a dyspneic, orthopneic and mildly cyanotic man. Pulse rate was 120, respirations 28 and blood pressure 150/80. There was slight cheilosis and the tongue had marginal reddening and papillary atrophy. The neck veins were engorged. There were basilar rales and moderate cardiac enlargement with a systolic gallop and no murmurs. There was mild liver enlargement, ascites, and moderate edema of the lower extremities. The deep reflexes were absent. Muscular tenderness and diminished sensation were present in the extremities.

Laboratory findings (see table 3): Gastric analysis after histamine revealed hypochlorhydria. Electrocardiogram showed borderline QRS voltage, inverted T_1, flat T_2. Roentgenogram of the chest revealed a cardiothoracic ratio of 16.5:29 cm. (fig. 2, *left*) and pulmonary congestion. Angiocardiography on the tenth day revealed a normal circulation rate, and a generalized cardiac enlargement, the wall of the left ventricle measuring 2.5 cm. in thickness.

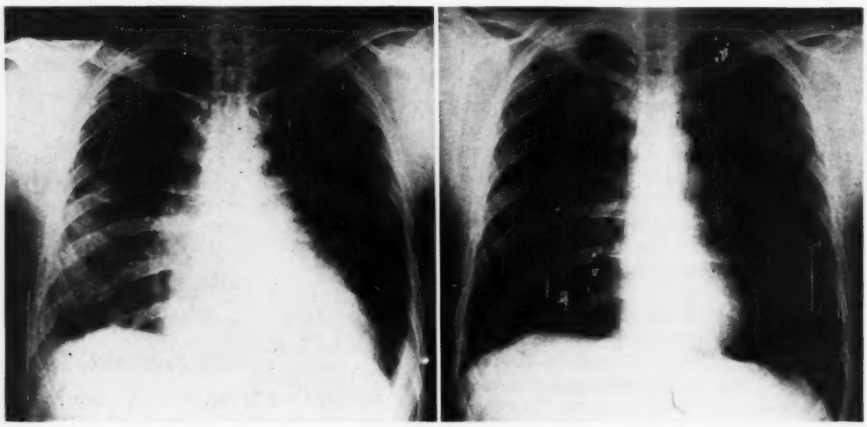

FIG. 2. Case 4. *Left.* Teleroentgenogram on 7/5/49. Cardiothoracic ratio 16.5:29 cm. *Right.* 9/7/49. Cardiothoracic ratio 11.1:29 cm.

Hospital Course. The patient was digitalized and given morphine and 4 cc. of Mercuhydrin in the first three days. Also, 10 mg. of thiamine was given intramuscularly daily for six days, after which the dose was doubled and large doses of all vitamins were given orally. Edema was absent after five days and by the eighth day he had lost 20 pounds. As the edema subsided the patient complained bitterly of hypersensitivity of the feet and toes and numbness of the extremities. Generalized muscular wasting became evident. The attending neurologist's diagnosis was B deficiency neuritis. Two cc. of crude liver extract were given daily from July 14 to July 26.

There was mental confusion on awakening during the first month, and a "heaviness of the chest" at bedtime, which was unrelieved by nitroglycerine. Electrocardiograms showed progressive inversion of the T wave in leads I and CF_4 in the first three weeks, suggesting myocardial infarction. The sedimentation rate was 22 mm. in one hour (Cutler) on Aug. 1 and 16 mm. on Aug. 15, 1949. Dicumarol was given from July 26 until Aug. 16. The cardiothoracic ratio decreased from 16.5:29 cm. on July 5 to 15.2:29 cm. on July 15 and 11.1:29 cm. on Sept. 7, 1949 (fig. 2, *right*). Adhesions were noted above the right hemidiaphragm on Sept. 7, 1949. Digitalis was discontinued on Sept. 26. Electrocardiograms after Oct. 10 were normal (fig. 3). Weakness, numbness and pain on walking persisted until the end of August. The blood pressure on August 22 was 150/86, and the pulse ranged from 80 to 90 at rest. Embryocardia persisted. Angiocardiography on September 2 revealed an unchanged circulation rate, and no change in the thickness of the wall of the left ventricle in spite of the spectacular decrease in heart size.

When discharged on Oct. 25, 1949 the patient still had weakness and minimal dyspnea on climbing stairs. When recalled on June 2, 1950 his appetite had increased and he had no dyspnea. He complained of numbness, tingling, and hypersensitivity of the feet. He appeared hyperkinetic and the tongue and fingers were tremorous. His pulse was 90 and his blood pressure, 128/90. The ankle jerks were absent and there was hypesthesia of the toes. Basal metabolic rates were minus 4 and minus 6 per cent. The cardiothoracic ratio was 11:29 cm. The electrocardiogram was normal (see figure 3).

Case 5. L. L., age 32, a cook, was admitted Jan. 8, 1950. He was disoriented. Relatives stated he had had palpitation and dyspnea for one year, and transient mental confusion for six months. Abdominal distention, nausea, cough and pleuritic chest pain appeared in the last two weeks. He had been drinking heavily for 15 years. For two years he had eaten poorly, and had consumed at least twelve bottles of beer daily, a fifth of whiskey on weekends, and often went three days without food.

Records of Army hospitalization from March 8, 1945 to Feb. 28, 1947 for a malunited fracture of the right femur revealed normal neurologic, cardiovascular, and renal findings.

In September 1948 a pension examination revealed hypesthesia and edema of both feet, absent right knee jerk, pulse 90, blood pressure 170/100 and a normal chest x-ray.

Examination revealed an obese, graying and orthopneic man who fabricated freely. Temperature was 99, pulse 120, respirations 30 and blood pressure 170/100. There were basilar rales and moderate cardiac enlargement with regular rhythm and no murmurs. The abdomen was distended. Bilateral pitting edema extended to the knees, and pigmentation was present on the right pretibial area. Areflexia and calf tenderness were noted. There was diminished sensation and weakness in all extremities.

Laboratory findings (see table 3): Spinal fluid was normal. Histamine gastric analysis two weeks after admission revealed hyperchlorhydria. Oral glucose tolerance curve was suggestive of diabetes.

Electrocardiogram showed flat or absent T waves in all leads. Teleroentgenogram of the chest revealed generalized cardiac enlargement and pulmonary congestion (fig. 4).

Hospital Course. On bed rest, and a diet containing 3 Gm. of sodium chloride, he lost 19 pounds in 48 hours, at which time there was no ankle edema. The liver was then palpable 4 cm. below the right costal margin, pulse was 108, blood pressure 150/100, and he appeared much improved. He had lost 32 pounds

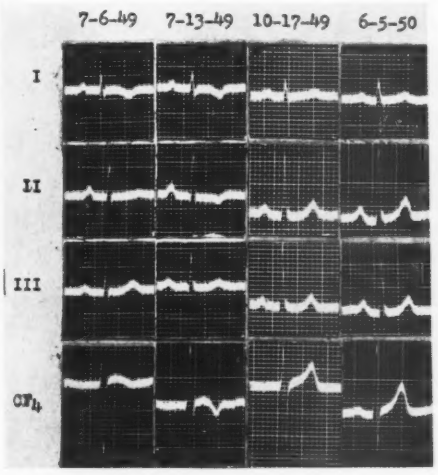

FIG. 3. Case 4. Transient T-wave changes for three weeks. Digitalis given for 13 weeks. Normal after 16 weeks.

by the fourth day and 36 pounds by the seventh day. A daily intramuscular injection containing 210 mg. thiamine, other soluble vitamins, and 2 cc. crude liver extract was given from the fourth to the eighteenth day. After the third week he received a high protein diet, large oral doses of all vitamins, 100 mg. thiamine intramuscularly daily, and vitamin B_{12} 15 μg. twice weekly.

Venous pressure on the fifth day was 12 cm. H_2O, and circulation time, arm-lung (ether) 5 seconds, and arm-tongue (Decholin), 14 seconds. On the nineteenth day arm-tongue time was 12 seconds.

Electrocardiograms on the fifth day revealed inversion of T waves in leads I, II, CF_2, and CF_5. On the eighth day these were upright, and the tracings were normal after three weeks (fig. 5). Teleroentgenograms revealed progressive decrease in cardio-

thoracic ratio from 17.5:31 cm. on admission to 15:31 cm. on the eighth day, and 13.5:31 cm. on the twenty-eighth day (fig. 4). The sedimentation rate five weeks after admission was 8 mm. in one hour.

From the second to fifth week the blood pressure ranged from 140/100 to 130/96, the pulse 100 to 128, with persistent embryocardia. After five weeks the mental status was normal except for mild memory defects. At this time the biceps jerks had returned, but the lower extremities remained areflexic. The patient left against advice on February 18, 1950.

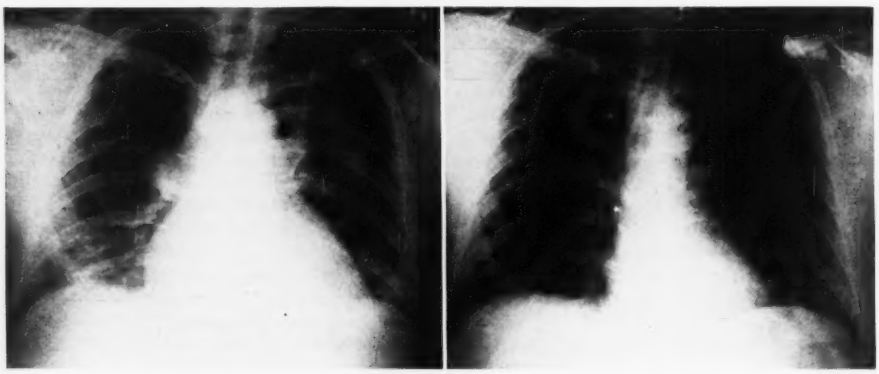

FIG. 4. Case 5. *Left.* Teleroentgenogram on 1/8/50. Cardiothoracic ratio 17.5:31 cm. *Right.* 2/6/50. Cardiothoracic ratio 13.5:31 cm.

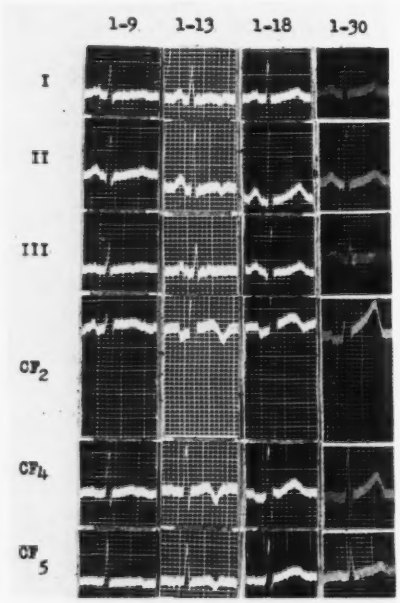

FIG. 5. Case 5. Transient inversion of T waves with return to normal in three weeks.

CLINICAL FEATURES OF CARDIOVASCULAR MANIFESTATIONS OF BERIBERI

Etiology. Clinical and experimental evidence has established that thiamine deficiency is responsible for beriberi.[3] Thiamine is a part of an essential enzyme of carbohydrate metabolism. The diets of the majority of patients who develop beriberi have been low in thiamine but of high caloric value. Diets consisting mostly or entirely of carbohydrates are especially harmful.[4, 5] It is currently estimated that an average young adult requires 0.25 to 0.35 mg. of thiamine per 1000 calories of balanced diet.[4] The importance of the intestinal synthesis of thiamine in the prevention of deficiency states has not been established.[4-7]

In the Occident, alcoholism and a thiamine-poor diet are jointly responsible for the majority of cases of beriberi.

The dietary history is usually unsatisfactory unless obtained and interpreted by a nutritionist.[2] Digestive disturbances may impair absorption or utilization of food and vitamins. Psychic or other illnesses which limit the choice of foods occasionally may create thiamine deficiency.[8, 9] Overcooking destroys thiamine. Increased metabolism due to thyrotoxicosis, exercise, pregnancy, or infections increases the demand for thiamine in proportion to the added caloric demand.[4] Increased metabolism also increases the heart load. In

48 cases studied by Blankenhorn, alcoholism was the main precipitating factor in 50 per cent, other diseases in 37.5 per cent and no evident cause was found in 12.5 per cent.[8]

All 5 patients here presented were white men between ages 32 and 39 who consumed excessive amounts of alcohol. The thiamine intake of each (diet and alcohol) had been approximately 0.15 to 0.26 mg. per 1000 calories.

Symptoms and Signs. The symptoms and signs vary with the duration and severity of hypovitaminosis and are modified by associated diseases. One patient in this series had concomitant active pulmonary tuberculosis, which others have reported.[3, 10] Beriberi has been classified as (1) "dry," or neuritic; (2) "wet," or edematous; and (3) "cardiac," which varies, but may be characterized by severe and fulminating cardiac symptoms.[11] Mixed forms of the disease are most frequently seen, and patients may display different forms of the disease at various times.[5] Severe polyneuritis is not usually associated with cardiac failure, probably because the neuritis prevents muscular exertion. Mild polyneuritis may permit severe congestive failure to develop rapidly, particularly in patients doing heavy work.[9, 10] The relationships of cardiac enlargement, edema and polyneuritis in these patients is shown in table 1.

One-third of patients with beriberi show evidence of cardiovascular dysfunction warranting a diagnosis of "beriberi heart."[8, 12] The 5 patients in this series had dyspnea, orthopnea, edema, hepatomegaly; 4 had elevated venous pressure, and 2 had paroxysmal nocturnal dyspnea. Three patients had palpitation and 3 had syncope prior to admission. Syncope is due to carotid sinus irritability and disappears with thiamine therapy.[9] Peripheral edema may be slight or extensive, and may be so evenly distributed, hard, and nondependent that the patient appears robust until he has lost 30 to 40 pounds of fluid.[11] Loss of edema is often attended by aggravation of the symptoms of polyneuritis. Tachycardia is nearly always present, and cardiac enlargement is the rule, though occasionally failure occurs in a heart of normal size.[3, 9] One patient in this series had no evidence of cardiac enlargement and only moderate dyspnea in the presence of marked edema, electrocardiographic changes, and severe polyneuritis. Embryocardia is frequently noted, and was present in the 2 patients in this series who had marked cardiac enlargement. One of these had gallop rhythm, another common finding. Transient systolic murmurs were heard in 2 of the 5 patients. An overactive heart with a bounding, Corrigan-like pulse, and elevated pulse pressure is found in one-third of patients, but cardiac activity and pulse contour may be normal.[10, 13] Blankenhorn[2] found pistol shot arterial sounds and elevated pulse pressure in only 2 of 9 patients, whereas Gelfand and Bellet[3] reported a Corrigan-like pulse in their 10 patients. Of the 5 patients reported here, 1 had a forceful apical impulse but none had a Corrigan pulse. Three had elevation of the systolic blood pressure, which disappeared during convalescence.

Studies of hemodynamics indicate a relatively rapid circulation in a majority of cases.[2, 9] This has been attributed to generalized arteriolar dilatation which creates a condition similar to multiple arteriovenous fistulas. This view is supported by the findings of rapid circulation time, decreased arteriovenous oxygen difference, and high pulse pressure.[3, 9, 14] Burwell and Dexter[14] demonstrated a rapid circulation and a high cardiac output in 1 case by means of cardiac catheterization, and showed a dramatic disappearance of these abnormalities after three weeks of therapy. There are, however, genuine cases in which a slow circulation has been demonstrated. Two of 10 patients in a series reported by Blankenhorn and co-workers[13] had markedly prolonged circulation times. This may be due to relatively severe myocardial degeneration with less arteriolar dilatation. In this series, the circulation time was relatively rapid in 1 case, only slightly prolonged in another, and a third had a normal circulation rate on the tenth day.

Symptoms of neuritis consist of aching and numbness of the calves, peripheral muscular weakness, or burning hypersensitive feet and fingers. Typical findings include symmetrical absence of reflexes, calf tenderness, inability to rise from a squat, and patchy or "stocking-and-glove" peripheral sensory loss, particularly

in the lower extremities. Severe cases show extreme muscular wasting. Psychosis is occasionally present. Polyneuritis was found in each patient. One had Korsakoff's psychosis, and 1 with severe neuritis was mildly confused. Symptoms and signs of neuritis became more apparent with loss of edema in 2 patients, and in another case were absent until diuresis occurred

The appearance of 2 patients suggested hyperthyroidism, but basal metabolic rates were normal. All had anorexia, 3 had abdominal soreness, and 1 had diarrhea in the later stages of his illness. One patient had cheilosis, 1 had scurvy, and 2 had mild glossitis.

X-Ray Findings. The heart shadow is usually diffusely enlarged. If irreversible damage has not occurred, the reduction in size during therapy may be striking. In this series 4 patients had cardiac enlargement, which disappeared with therapy. Angiocardiograms in case 4 revealed dilatation and thickening of the wall of the left ventricle, which decreased markedly during two months of therapy.

Electrocardiogram. Electrocardiographic changes are not specific, are often minor, and occasionally are absent.[9, 10, 13] Usually there is a sinus rhythm with low voltage of T or QRS or inversion of T waves in one or more limb or precordial leads. Prolongation of the Q-T interval occurs less frequently, and occasionally premature contractions, auricular fibrillation, or bundle branch block is present. The temporary accentuation of T wave changes during therapy, such as occurred in 2 patients, may suggest coronary occlusion.[9, 10, 15] Reversion to normal usually occurs within three to four weeks, lagging behind clinical recovery. In this series, 4 patients had flat or inverted T waves in one or more leads. Two had low voltage of the QRS complex. Two had normal tracings, but in one of these the inverted T_3 became upright during therapy. One patient's electrocardiogram became normal in three weeks, and the tracings of 2 patients reverted to normal in less than three months, but the exact time of reversion is unknown. A fourth patient (case 2) had residual abnormalities after six months of treatment.

Laboratory Findings. Hypoproteinemia and anemia are usually found, and evidence of hepatocellular damage is occasionally observed.[2, 9, 13] Four patients had moderate anemia, and 2 of 4 patients tested had hypoproteinemia. The milder degrees of anemia disappeared with diuresis. Liver function tests showed only mild bromsulfalein retention in 3 patients. Another had abnormalities suggesting early cirrhosis. One patient had hypochlorhydria, and 2 had hyperchlorhydria. One had impaired glucose tolerance. Three patients had unexplained mild elevation of the sedimentation rate during the first month. Two of these had x-ray signs suggestive of pneumonitis. The susceptibility of these patients to respiratory infections and the greater likelihood of sudden death in such cases has been noted.[8, 9]

Diagnosis. Blankenhorn states that patients with slow circulation may closely resemble other forms of degenerative heart disease, but the diagnosis can be made with relative certainty utilizing the combined skills of the nutritionist, cardiologist, and neurologist. The patients in this series conform for the most part to Blankenhorn's criteria (tables 1 and 2). All had evidence of cardiac failure associated with polyneuritis, and no evidence of coronary, rheumatic, syphilitic or thyrotoxic heart disease. Although none of these patients had a control period of thiamine free diet, their response to therapy was typical of beriberi heart disease.

In the differential diagnosis hyperthyroidism, arteriovenous fistula, Fiedler's myocarditis, idiopathic postpartum failure, glomerulonephritis, cirrhosis, lupus erythematosus, scleroderma, periarteritis nodosa and amyloidosis must be considered.

Morbid Anatomy. In chronic thiamine deficiency the heart may be hypertrophied as well as dilated. Wenckebach and others in the Orient observed more right than left heart dilatation.[9, 10] This is not the rule.[9]

Microscopically, vacuolization (hydropic degeneration) of the myocardial fibers, collagenous infiltration, edema, fragmentation, loss of striation, and longitudinal separation of muscle fibers are observed. In severe chronic

cases, considerable interstitial fibrosis is present. These changes may be absent. Degenerative lesions also occur in the nervous system, especially in peripheral nerves.

Treatment. In many cases rest and the usual hospital diet may result in striking improvement within a few hours.[10,13] Four patients in this series had moderate improvement of signs of congestive failure before parenteral thiamine was given. Specific therapy consists of the parenteral administration of thiamine in doses of 10 to 100 mg. daily. Oral therapy alone may result in relapse. A high-protein diet should be given, with oral and parenteral supplements of all vitamins. Associated pellagra or scurvy require large doses of niacin or ascorbic acid. Excessive and unbalanced administration of vitamins may precipitate other avitaminoses.[6] Digitalis is indicated if the heart is markedly dilated, and mercurial diuretics and moderate sodium restriction are indicated in markedly edematous patients.[3] Thiamine has produced dramatic response when digitalis and mercurials failed.[9] In this series, the time of disappearance of edema and symptoms of congestive failure varied from 7 to 10 days, but 2 patients (excluding the patient with tuberculosis) had persistent tachycardia for several weeks. The time required for maximal decrease in heart size varied from one to two months. The loss of edema may have been accelerated in 4 instances by sodium restriction. Other authors have commented on the variable response to treatment. In general, the neuritis responds much more slowly than the cardiovascular manifestations. In severe chronic cases, even prolonged intensive therapy may result in only slow and incomplete recovery.

Summary and Conclusions

1. Beriberi heart disease occurs in Iowa.

2. Five alcoholic patients with variable amounts of cardiac failure, polyneuritis and cardiac enlargement which conform to the criteria for diagnosis of beriberi heart disease have been presented.

3. Because beriberi is a reversible form of heart disease, as shown by these 5 patients, its early diagnosis is important.

Addendum

Case 2, R. S., was admitted again on Dec. 7, 1950 with minimal cardiac failure, mild neuritis and acute alcoholism. The cardiothoracic ratio was 17:32 cm. as compared to 13.5:32 cm. in Nov. 1949; the tuberculous lesions were unchanged and pneumoperitoneum was absent. Electrocardiogram was now normal. After one week on a thiamine-poor diet there was no change in these findings; the venous pressure was 15 cm. of H_2O and the arm-to-tongue time was 8 seconds. He was then given 120 mg. of thiamine daily. Edema gradually cleared, and on the eleventh day of therapy flattening of the T waves was noted in all leads. On the eighteenth day the T waves in leads I, AV_L, V_4, V_5, V_6 were inverted or diphasic, and the cardiothoracic ratio was 15.5:32 cm. Five days later he was again transferred to a tuberculosis sanatorium.

Comment: Cardiac enlargement and elevated venous pressure was, therefore, found in all 5 patients; 4 had a normal or only slightly prolonged circulation time, and had electrocardiographic changes during therapy.

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Mural Thrombosis and Arterial Embolism in Mitral Stenosis

A Clinicopathologic Study of Fifty-one Cases

By ROBERT A. JORDAN, M.D., CHARLES H. SCHEIFLEY, M.D., AND JESSE E. EDWARDS, M.D.

A clinicopathologic study of 51 cases of mitral stenosis with intracardiac mural thrombi is presented with particular reference to the locations of these thrombi and their relationship to the associated thromboembolic phenomena. In 27 cases the thrombi were present only in the left side of the heart, in 15 cases they were in both sides of the heart, and in 9 cases they were present only in the right atrium. Of 42 cases in which thrombi were located in the left side of the heart, in 20 the thrombi were limited to the left auricular appendage. In the remaining 22 cases in this group the thrombi in the left side of the heart were situated on the main atrial wall, in the auricular appendage and on the main atrial wall together, or in the left ventricle. Systemic arterial emboli occurred frequently regardless of the particular site in the left side of the heart at which the thrombus formed. Of 24 cases in which thrombi were situated in the right side of the heart, in 20 the thrombi were restricted to the right auricular appendage.

ARTERIAL embolism is a frequent and sometimes fatal complication of mitral stenosis. Willius[13] stated that emboli are present in 30 per cent of all cases of mitral stenosis in which death is due to myocardial failure. Weiss and Davis[11] found pulmonary or visceral infarcts at necropsy in 45 per cent of 164 patients who died from rheumatic heart disease. In addition these authors studied 48 consecutive patients who had cerebral emboli and found rheumatic heart disease in 23 instances. Bull[2] in a necropsy study found severe mitral stenosis in 5 of 15 cases in which arterial embolism of the extremities occurred.

Most of the arterial emboli occurring in patients with mitral stenosis arise from mural thrombi in the left atrium.[2, 5, 14] Intracardiac mural thrombi were present in nearly a third of 116 cases of severe rheumatic heart disease studied at necropsy by Garvin.[4] Several workers[4–6] have demonstrated that the intracardiac mural thrombi in mitral stenosis are situated predominantly in the atria, particularly in the left atrium. Rarely do mural thrombi occur in the ventricles in mitral stenosis.

The impression is gained from the writings of Welch,[12] Bull and others that it is rare for atrial mural thrombi to be found anywhere except in the auricular appendages. A review of the literature disclosed three studies on the mural thrombi in mitral stenosis wherein the exact locations of these thrombi were designated. In the study by Graef and associates[5] there were 19 cases of mitral stenosis in which left atrial mural thrombi occurred. In only 9 of these 19 cases were the thrombi limited to the left auricular appendage. In the same study there were 10 cases in which there were right atrial thrombi, all of which were found in the auricular appendage. Of the 5 cases of mitral stenosis in which there were left atrial thrombi, reported by Bull, in 3 cases the thrombi were limited to the auricular appendage. There were left atrial mural thrombi in 50 cases of rheumatic heart disease in the study reported by Söderström.[10] Mural thrombi were found in the left auricular appendage in 29 instances, and on the main left atrial wall in 25 instances. No statement was made as to the number of cases in which thrombi in the left auricular appendage and on the main left atrial wall coexisted.

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The exact location of the intracardiac mural thrombi occurring in mitral stenosis is a consideration of current interest. Surgical removal of the left auricular appendage has been suggested as a possible means of reducing the hazard of recurring arterial emboli in patients with mitral stenosis. Madden[9] has reported on 2 patients with mitral stenosis and recurring arterial emboli in whom he resected the left auricular appendage. In 3 patients with similar conditions Baronofsky[1] ligated the left auricular appendage. Resection of one or both auricular appendages has been performed successfully in dogs.[3, 8]

The present study was stimulated by the desire to determine if there is a sound pathologic basis for the proposal that the left auricular appendage be ligated or resected to prevent the recurrence of arterial emboli in patients with mitral stenosis. It is a clinical and pathologic analysis of 51 cases of mitral stenosis in which intracardiac mural thrombi were found at necropsy.

Material

The 51 cases used for this study included all cases of mitral stenosis with intracardiac mural thrombi found in a series of 11,536 necropsies performed at the Mayo Clinic during the 20 year period ending Dec. 31, 1948. All cases of bacterial endocarditis and all cases in which there was gross evidence of ventricular myocardial infarction were excluded from the study. Mitral stenosis of a moderate to severe degree was present in all cases. In several instances there were associated rheumatic lesions of the aortic or the tricuspid valve, or of both.

The average age of the 51 patients at the time of death was 45 years. The ages ranged from 17 years to 83 years. The majority of the patients died during the fourth, fifth and sixth decades of life. There were only 9 patients who were 60 years of age or older at the time of death.

Distribution of Mural Thrombi

The distribution of mural thrombi according to the side of the heart in which they were found is given in table 1.

In certain cases the left atrial mural thrombi were limited to the left auricular appendage; in other cases they were present only on the main left atrial wall; and finally in some cases they were in both locations.

Of the 27 cases in which mural thrombi were present only in the left side of the heart, in 10 the thrombi were restricted to the left auricular appendage. Of the remaining 17 cases, in 10 the thrombi were found both in the auricular appendage and on the left atrial wall, in 4 they were found only on the main left atrial wall, in 2 they were found only in the left ventricle, and in 1 case they were found in the auricular appendage, on the left atrial wall and in the left ventricle. In the 15 cases in which the thrombi were present in both sides of the heart, there were 10 instances in which the thrombi in the left side were restricted to the left auricular appendage. There were thrombi on the left atrial wall alone in 2 of the 15 cases, and in the auricular appendage and on the main left atrial wall in 3 cases. Thus in 42 cases mural thrombi were present in the left side of the heart, but in only 20 of the 42 cases were they restricted to the left auricular appendage.

Table 1.—*Distribution of the Mural Thrombi in 51 Cases of Mitral Stenosis*

Location of thrombi	Cases
Left side of heart only	27
Right and left sides of heart	15
Right side of heart only (all in right atrium)	9
Total	51

A somewhat different distribution was found for the mural thrombi occurring in the right atrium. In 15 cases mural thrombi in the right atrium were associated with thrombi in the left side of the heart. In 11 of these 15 cases the right atrial thrombi were restricted to the auricular appendage. In 9 additional cases in which mural thrombi were present only in the right atrium, the thrombi were limited to the auricular appendage. Thus in a total of 24 cases in which right atrial mural thrombi were present, there were 20 cases in which the auricular appendage was the only site of mural thrombosis in the right side of the heart.

Thromboembolic Phenomena

Pathologic evidence of systemic arterial embolization was present in 32 of the 51 cases studied. In 21 of these cases there were arterial

emboli to two or more organs, and in 17 of the 32 cases there were pulmonary infarcts or emboli in addition to the systemic arterial emboli. The incidence and distribution of emboli to various organs are shown in figure 1. The mural thrombi in the left side of the heart were restricted to the left auricular appendage in only 13 of the 32 cases in which there were systemic arterial emboli (table 2). In 4 of the 32 cases there were no mural thrombi in the left side of the heart.

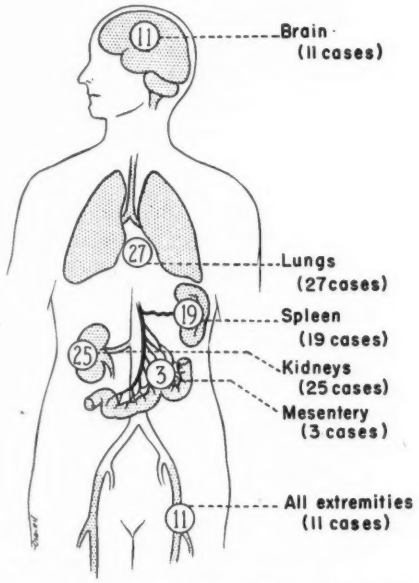

FIG. 1. Distribution and incidence of emboli in 51 cases of mitral stenosis with intracardiac mural thrombi.

There were 15 patients in this study who had clinically recognized systemic arterial embolic episodes. In 5 of these patients the emboli had been the major or a contributory cause of death. There were emboli to more than one organ in 14 of the 15 cases. Peripheral arterial emboli were present in 11 cases, cerebral emboli in 9 cases, and mesenteric arterial emboli in 3 cases. The mural thrombi in the left side of the heart were limited to the left auricular appendage in 8 of the 15 cases (table 3).

Pulmonary emboli or infarcts were present at necropsy in 27 cases, in 16 of which mural thrombi were found in the right atrium. Peripheral venous thrombi were found in 8 cases, in 5 of which they were associated with right atrial mural thrombi. In 8 cases no source of pulmonary embolism was found at necropsy.

There were 5 cases of fatal pulmonary embolism. In all 5 cases there were mural thrombi in the right atrium, in 3 of which thrombi were demonstrated in the peripheral veins as well.

TABLE 2.—*Distribution of the Mural Thrombi in the Left Side of the Heart in 32 Cases of Mitral Stenosis with Systemic Arterial Emboli*

Location of thrombi	Cases	Per cent
Left auricular appendage only	13	40.6
Left auricular appendage and main left atrium	8	25.0
Main left atrium only	5	15.6
Left ventricle only	2	6.3
No thrombi present in left side of heart	4	12.5
Total	32	

TABLE 3.—*Distribution of the Mural Thrombi in the Left Side of the Heart in 15 Cases of Mitral Stenosis with Clinically Recognized Systemic Arterial Emboli*

Location of thrombi	Cases	Per cent
Left auricular appendage only	8	53.3
Left auricular appendage and main left atrium	4	26.7
Main left atrium only	2	13.3
No thrombi present in left side of heart	1	6.7
Total	15	

TABLE 4.—*Incidence of Thrombi Limited to the Left Auricular Appendage in Mitral Stenosis with Mural Thrombi in the Left Side of the Heart*

Author	Total cases	Thrombi limited to left auricular appendage	
		Cases	Per cent
Bull	5	3	60.0
Graef and associates	19	9	47.4
Present study	42	20	47.6
Total	66	32	48.5

Cardiac Rhythm

Several authors [4, 5, 7, 11] have pointed out that intracardiac mural thrombi occurring in mitral stenosis are usually associated with auricular fibrillation. In this study the cardiac rhythm was known in 50 of the 51 cases studied. In 42 of these 50 cases there were physical signs of auricular fibrillation. The diagnosis was confirmed by electrocardiographic studies in 38 of the 42 cases; no electrocardiograms had been taken in the remaining 4 cases.

Congestive Cardiac Failure

It has been stated by several authorities [4, 13] that the incidence of mural thrombosis in all types of cardiac disease including mitral stenosis is higher in those patients who have had congestive cardiac failure than in those who have not had cardiac failure. Forty-seven patients in this study either had had congestive cardiac failure at the time of the final hospital admission or had had a history of previous episodes of congestive failure; 4 patients gave no history of such failure. Of these 4 patients, the left atrial mural thrombi were restricted to the left auricular appendage in 3, to the main left atrial wall in 1.

Comment

From the data presented in this study and from the studies of Bull, of Graef and associates, and of Söderström, it seems reasonable to conclude that mural thrombi occurring in the left side of the heart in mitral stenosis are restricted to the left auricular appendage in approximately half of the cases (table 4). It would thus appear that resection or ligation of the left auricular appendage of patients with mitral stenosis and recurring arterial emboli would probably offer no more than a 50 per cent chance of eliminating the source for systemic arterial emboli.

A somewhat different situation exists with regard to the predominant locations of the right atrial thrombi in mitral stenosis. In our study as well as that of Graef and associates the right atrial thrombi were in most instances restricted to the right auricular appendage. It should be remembered, however, that in our study, while 16 of the 27 patients with pulmonary emboli had mural thrombi in the right atrium, 8 of these 27 patients had thrombi also in the peripheral veins.

The reason for the frequent occurrence of mural thrombi on the main wall of the left atrium in mitral stenosis is not definitely known. It seems probable that the MacCallum patches or endocardial pockets, so often found in the left atrial wall in mitral stenosis, may be the site of origin of mural thrombi.

Summary and Conclusions

1. A clinicopathologic study of 51 cases of mitral stenosis with intracardiac mural thrombi is presented, with particular reference to the incidence and location of the mural thrombi and the associated thromboembolic phenomena.

2. In mitral stenosis mural thrombi are found most frequently in the atria, and approximately twice as often in the left as in the right atrium.

3. Only about half of the mural thrombi in the left side of the heart are restricted to the left auricular appendage.

4. The majority of the right atrial thrombi in mitral stenosis are restricted to the right auricular appendage.

5. Systemic arterial emboli were found with approximately the same frequency whether the mural thrombi were restricted to the left auricular appendage or were located elsewhere in the left side of the heart.

6. In patients with mitral stenosis and mural thrombosis there is a high incidence of auricular fibrillation.

7. The majority of patients with mitral stenosis who are found to have intracardiac mural thrombi at necropsy have had congestive cardiac failure at some time during life.

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Variations in Electrocardiographic Responses during Exercise

Studies of Normal Subjects under Unusual Stresses and of Patients with Cardiopulmonary Diseases

By PAUL N. G. YU, M.D., ROBERT A. BRUCE, M.D., FRANK W. LOVEJOY, JR., M.D., AND MARION E. MCDOWELL, M.D.

Precordial electrocardiograms were taken before, during, and after exercise in 20 normal subjects and in 48 patients with cardiopulmonary diseases. Analysis of the findings was based on changes in Q-T interval, alterations in QRS, RS-T and T waves and on presence or absence of premature beats. Whereas in performing standard tests, normal subjects showed no evidence of coronary insufficiency, in about two-thirds of the patients abnormal changes were demonstrable. Definite RS-T depression and changes in Q-T interval were also observed in normal subjects under unusual stresses. The electrocardiographic changes during exertion were discussed and emphasized.

THE CHANGES of the Q-T interval during and after exercise in normal subjects, and in patients with cardiopulmonary diseases, have been described in a previous communication.[1] Level walking was done on a motor driven treadmill for 10 minutes, or less if markedly disabled, at a pace of either 1.73 or 2.60 miles per hour. In normal subjects the corrected Q-T interval was prolonged during exercise, shortened during early recovery and then returned to resting value during late recovery. The Q-T:T-Q ratio increased about 40 per cent during exercise and it returned promptly (to resting value) during early recovery. There were no significant changes in the RS-T segment or T wave. In patients with cardiopulmonary diseases, the changes in the Q-T interval showed somewhat different patterns. The frequency of abnormal response in the Q-T interval varied inversely with the duration of exercise. Furthermore, in all the cases in which there was distinct S-T depression during or after exercise, an abnormal response in the Q-T interval was also observed.

Since then, similar studies have been made in normal subjects and in patients walking on the treadmill at 1.73 miles per hour and 10 per cent grade, which is considered as the standard exercise test in this laboratory.[2] Additional observations were also made in normal subjects with increased work load (20 per cent grade) or induced anoxemia, or both. The purpose of this report is to describe the electrocardiographic changes of the normal subjects under different stresses and to compare them with those obtained in the patients. The cardiorespiratory changes are described separately.[3]

METHODS AND MATERIAL

The method of taking chest lead electrocardiograms was essentially the same as that described previously.[1] The only difference was that the resting period has been reduced from 10 minutes to 5 minutes, hence consecutive resting electrocardiograms were taken in the second, third, and fourth minutes at rest. During exercise a tracing was taken each minute up to the arbitrary limit of 10 minutes, or for the duration of tolerance as determined by each patient unable to walk 10 minutes. During the 10 minute period of recovery electrocardiograms were obtained in the first three and the last three minutes. The heart rates were

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obtained either by means of an electronic pulse counter, or by measuring the total QRS complexes in six consecutive seconds times 10. The cycle length and the Q-T interval of at least three consecutive complexes in each tracing were measured. The T-Q interval equalled the difference of corresponding cycle length and Q-T interval. The corrected Q-T (Q-T_c) or K is derived from the modified Bazett formula.[3]

Seven healthy male subjects between the age of 28 and 52 (6 physicians and 1 technician) who walked on the treadmill ergometer under different stresses served as normal controls. The speed of the treadmill was fixed at 1.73 miles per hour; the grade was 0 per cent, 10 per cent and 20 per cent respectively, and the inspired oxygen tension varied between 146 mm. Hg (room air) and 80 mm. Hg (11.3 per cent oxygen). The combination of the grade and inspired oxygen tension for the tests were grouped as follows:

Test Group	*Grade*	*Inspired O_2 Tension*
I	0%	146 mm. Hg
II	10%	146 mm. Hg
III	20%	146 mm. Hg
IV	10%	104 mm. Hg
V	20%	104 mm. Hg
VI	10%	80 mm. Hg

An additional 13 normal subjects (11 men and 2 women) between the ages of 21 and 56 years, were included with those of group II to make a total number of 20 controls and 26 tests (6 subjects walked twice) for the comparison with the patients.

Altogether 63 exercise tests with satisfactory electrocardiograms were made on 48 patients. The patients were divided into four groups: (a) arteriosclerotic and hypertensive heart diseases (ASHD and HHD), 10 (15 tests); (b) congenital heart diseases (CHD), 9 (11 tests); (c) pulmonary diseases (PD), 7 (8 tests); and (d) other conditions including thyrotoxicosis, rheumatic heart disease, polycythemia, anemia, 22 (29 tests). Disability of the patients is classified in two broad categories: (a) "none to moderate"—for those who were able to walk for the full 10 minutes, (b) "marked"—for those who were unable to walk 10 minutes.

The criteria of the abnormal response in the electrocardiograms for the standard exercise test were as follows:

(1) Q-T patterns: (a) Decrease in Q-T_c during exercise, or increase in Q-T_c during early recovery. (b) Q-T:T-Q ratio greater than 2 during exercise.

(2) RS-T and T patterns: (a) Depression of the RS-T segment greater than 1 mm. during exercise or recovery. (b) Marked increase in the voltage, or inversion of the T wave, during exercise.

(3) Premature beats: Multiple ventricular premature beats during exercise and early recovery.

Results

Normal Subjects

The mean values of the heart rate, Q-T_c and Q-T:T-Q ratio of the 7 normal subjects under different stresses are presented in table 1. The mean values of the Q-T_c and Q-T:T-Q ratio in consecutive minutes for the tests of groups II, III, IV, and V are also plotted in figure 1.

The over-all change of the Q-T_c in all the tests was prolongation during exercise, shortening during early recovery, and returning to resting value, or slight prolongation, during later recovery. The prolongation of Q-T_c during late recovery was more marked with severe stress than with moderate stresses. The Q-T_c pattern of the standard test (group II) was not materially different from that seen in level walking. When the work load was increased, or anoxemia induced, there was a tendency for the Q-T_c to decline during the last four minutes of exercise (fig. 1). The declination was similar to that observed in cases with hypertensive heart disease. This was further supported by the fact that in normal subjects under severe stress (group VI) the systolic blood pressure during exercise may reach 200 mm. Hg.

The Q-T:T-Q ratio varied directly with the heart rate and pulse pressure. The resting Q-T:T-Q ratio of the normal subjects was about 1.0 while breathing air and it was slightly higher when breathing 11.3 per cent oxygen. In groups I and II, the ratio was always less than 2 during exercise and promptly returned to the resting value during early recovery. With increased work load or induced anoxemia the Q-T:T-Q ratio during exercise was either greater than 2, or it did not return promptly to resting value in the first three minutes of recovery. During late recovery the ratio was still high (groups V and VI), although the heart rate was only 100 per minute.

No changes in the RS-T segment were demonstrable in all the normal subjects of the groups I and II. Only one subject of groups III and IV, respectively, showed slight RS-T depression during exercise. Whereas only slight to moderate RS-T depressions occurred during

exercise in all the subjects of group V, a very marked depression (sometimes as much as 4 mm.) was observed in those of group VI. In the latter individuals the RS-T depression the voltage of the T wave during exercise occurred on only three occasions. High, peaked T or inverted T waves during exercise were never observed.

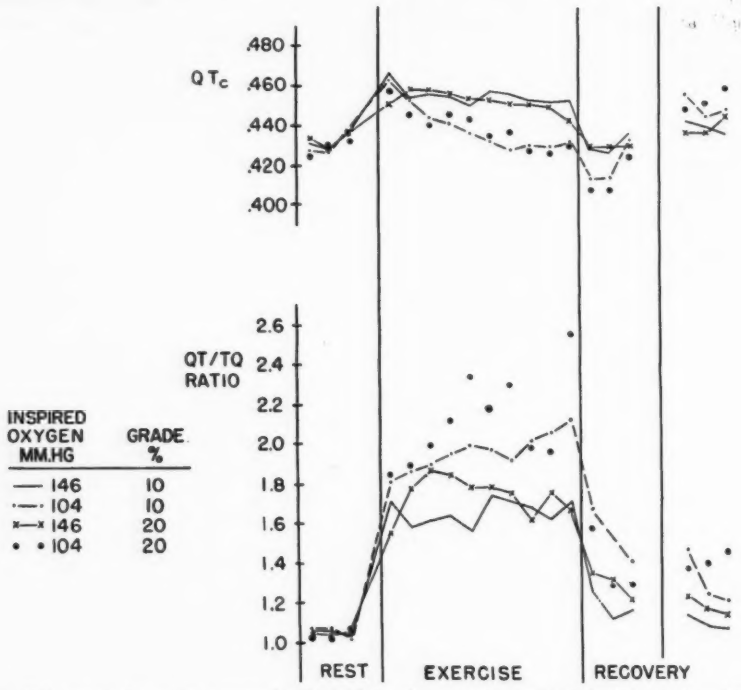

FIG. 1. This graph shows the composite data of the changes of corrected Q-T interval and Q-T:T-Q ratio during rest, exercise, and recovery in a group of seven normal subjects under different stresses.

TABLE 1.—*Mean Values of the Heart Rate, Q-T_c, and Q-T:T-Q Ratio during Exercise in 7 Normal Subjects under Different Stresses.*

Test Group	Grade %	Insp. pO_2 mm. Hg.	Heart Rate per minute				$Q\text{-}T_c\left(\frac{Q\text{-}T}{\sqrt{R\text{-}R}}\right)$				Q-T/T-Q			
			Rest	Exer.	Early Rec.	Late Rec.	Rest	Exer.	Early Rec.	Late Rec.	Rest	Exer.	Early Rec.	Late Rec.
I	0	146	77	90	80	78	.436	.448	.427	.435	0.97	1.21	1.00	0.99
II	10	146	82	115	96	87	.432	.455	.427	.440	1.03	1.66	1.18	1.11
III	20	146	82	137	115	94	.431	.439	.421	.450	1.04	1.96	1.36	1.32
IV	10	104	81	119	101	91	.433	.452	.430	.441	1.02	1.75	1.30	1.19
V	20	104	83	146	121	100	.429	.439	.412	.452	1.04	2.15	1.39	1.41
VI	10	80	89	136	112	101	.433	.451	.435	.450	1.15	2.15	1.47	1.43

usually persisted for three to six minutes during recovery. Elevation of the RS-T segment was never observed.

The voltage of the T wave usually became slightly lower during exercise and slightly higher during recovery. A minimal increase in

Throughout the tests there was no significant change in the QRS complex, nor was any ventricular premature beat recorded.

Representative tracings of a normal subject under different stresses showing the various changes are reproduced in figure 2.

Patients

The incidence of the abnormal electrocardiographic changes in 48 patients with various cardiopulmonary diseases are summarized in table 2, with 20 normal subjects serving as controls.

there was a definite reduction in the voltage of the R waves, and an increase in the amplitude of QS waves. In 2 cases the T wave became high and peaked during exercise.

In patients making up the group with congenital heart disease a characteristic con-

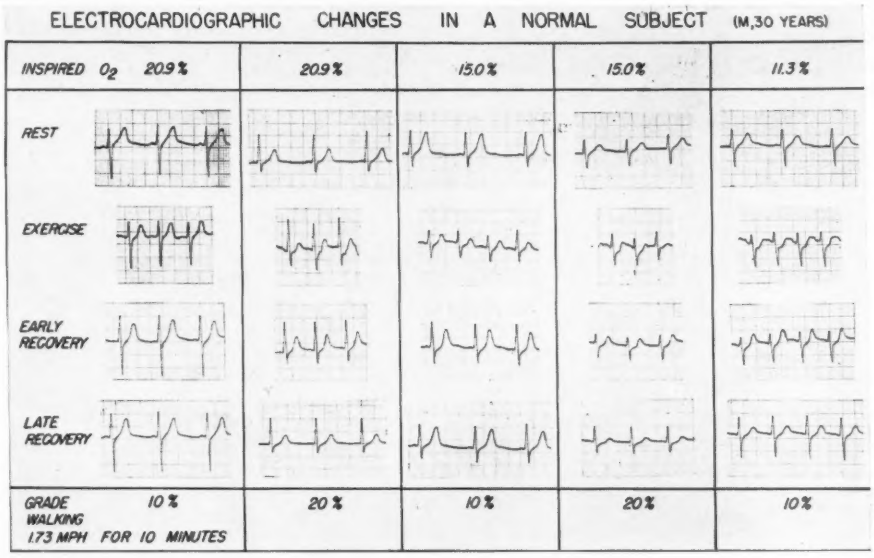

FIG. 2. This graph shows illustrative electrocardiographic tracings during rest, exercise, and recovery in a normal subject under various stresses. The description of changes is in the test.

TABLE 2.—*Comparison of the Abnormal Electrocardiographic Changes between 20 Normal Subjects and 48 Patients.*

	No. of Subjects	$Q\text{-}T_c\left(\frac{Q\text{-}T}{\sqrt{R\text{-}R}}\right)$		Q-T/T-Q		ST-T Wave		Premature Beats	
		No. of Tests	No. Abnormal	No. of Tests	No. Abnormal	No. of Tests	No. Abnormal	No. of Tests	No. Positive
Normal Controls	20	26	0	26	0	26	0	26	0
ASHD and HHD	10	15	5	15	9	15	11	15	1
Congenital Heart Disease	9	11	10	11	5	11	0	11	2
Pulmonary Disease	7	8	4	8	3	8	1	8	0
Miscellaneous Group	22	29	8	29	12	29	4	29	0

In the group of patients with arteriosclerotic and hypertensive heart disease, RS-T depressions during and after exercise were most frequently observed, followed by high Q-T:T-Q ratio during exercise. Abnormal $Q\text{-}T_c$ was noted in 5 of 15 tests and ventricular premature beats occurred in only one case. In another patient (R. W., case 23) during exercise

genital pattern of the $Q\text{-}T_c$ change, i.e., decrease during exercise and increase during early recovery, was observed in 8 of 9 cases. The exception was a patient with coarctation of the aorta. High Q-T:T-Q ratio during exercise was noted in 3 cases and the presence of ventricular premature beats in 2 cases. There was no significant change in either RS-T segment or T wave.

In the patients with pulmonary disease, an abnormal Q-T_c response was observed in 3, high Q-T:T-Q ratio in 2, and RS-T depression in 1 patient.

The patients in the miscellaneous group showed variable responses. High Q-T:T-Q ratios were most frequent, and an abnormal Q-T_c pattern and RS-T depression were less common. High, peaked T wave during exercise was seen in one case. The electrocardiographic response in patients with compensated rheumatic heart disease was usually normal, except for an occasional high Q-T:T-Q ratio during exercise.

TABLE 3.—*Comparison between the Changes in Q-T Pattern and RST-T Waves in 63 Tests among Patients.*

Electrocardiographic Changes	No. of Test	Per Cent
Abnormal Q-T and normal RST-T.	25	40
Abnormal RST-T and normal Q-T.	8	12.7
Both Q-T and RST-T abnormal...	9	14.3
Both Q-T and RST-T normal.....	21	33
Total.....	63	100

The comparison between the incidence of abnormal Q-T changes and that of abnormal RST-T changes in 48 patients is tabulated in table 3. Whereas in 40 per cent of the tests there were definite changes in Q-T interval without any alteration of RST-T waves, in only 12.7 per cent were there abnormal RST-T changes with normal Q-T response. Both abnormal Q-T and RST-T changes were observed in 14.3 per cent and finally in the remaining 33 per cent there was neither Q-T nor RST-T change.

Furthermore, there was an inverse relationship between the incidence of abnormal electrocardiographic response (both Q-T pattern and RST-T changes) and the duration of exercise. Of patients who walked the full 10 minutes, 19 of 36 tests (52 per cent) showed electrocardiographic abnormalities, whereas of those who walked less than 10 minutes, 23 of 27 tests (85 per cent) were abnormal.

Case reports of 9 patients are briefly presented in the following section with reproduction of the electrocardiograms in figures 3 and 4 for illustration of the types of responses seen.

Case Reports

(1) G. E. H. This 58 year old man had a history of exertional dyspnea and recurrent lower left chest pain. He was about 25 pounds overweight and quite anxious about his symptoms. Physical examination, x-ray, and resting electrocardiogram were essentially negative. Exercise tolerance for the full 10 minutes showed some increased voltage of the T waves in the chest lead electrocardiogram. This change was considered to represent early coronary insufficiency due to subendocardial ischemia.

(2) S. E. This 52 year old physician had been in good health until about one year ago when some exertional substernal discomfort was noticed. His family history was of importance in that his father, two paternal uncles and a younger brother had coronary occlusion. Physical examination was essentially negative except for a few basilar rales. Fluoroscopy of the chest and electrocardiogram at rest were normal. Exercise tolerance test for full 10 minutes showed definite S-T depression in the chest lead electrocardiogram after the fifth minute of exercise and during early recovery. This electrocardiographic change was compatible with the classical features of angina pectoris.

(3) R. W. This 53 year old man had a history of pain of angina pectoris for three years, which was definitely benefited by the administration of nitroglycerine. He was about 25 pounds over his ideal weight. Exercise tolerance test for full 10 minutes showed borderline physical fitness index and very marked electrocardiographic changes. During exercise there was a definite reduction in the voltage of the R wave and increase in QS wave. In addition, there was also S-T depression followed by high T wave. The S-T depression persisted for six minutes after exercise. Although the history suggested only angina pectoris, the electrocardiographic changes during exercise simulated an anterior myocardial infarction. This abnormality disappeared with recovery.

(4) N. L. This 60 year old woman had recurrent episodes of substernal pain with radiation to the arms for the past eight years. Six years ago she was treated for myocardial infarction. She had been hypertensive for several years. She was able to walk for only six minutes when she became tired, dyspneic and subsequently on sitting down felt a stinging pain in the left shoulder for several minutes. Blood pressure rose to 200/120 at this point. During exercise she exhibited a paradoxic response in the respiratory efficiency. There was a significant depression of the S-T segment in the resting chest lead electrocardiogram, which became more marked during exercise, and persisted for several minutes thereafter. In this patient, an abnormal electrocardiographic finding was accentuated by exertion.

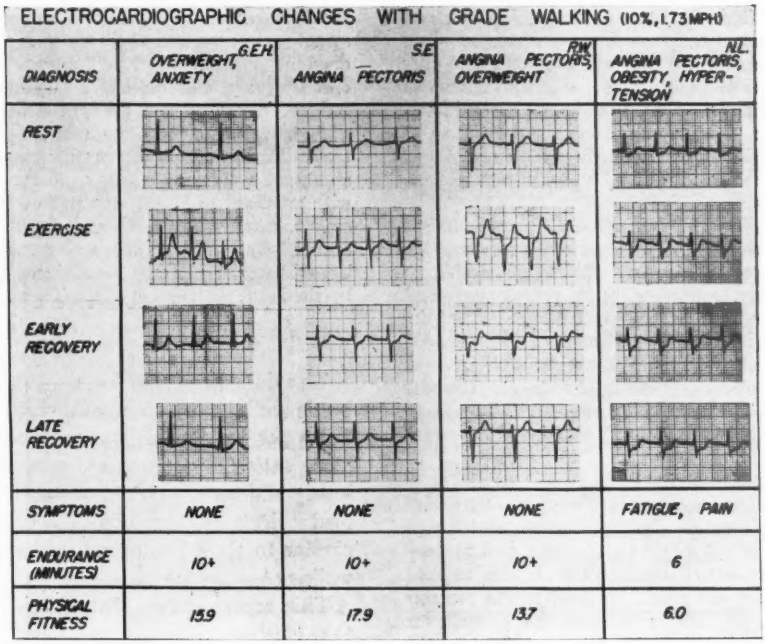

FIG. 3

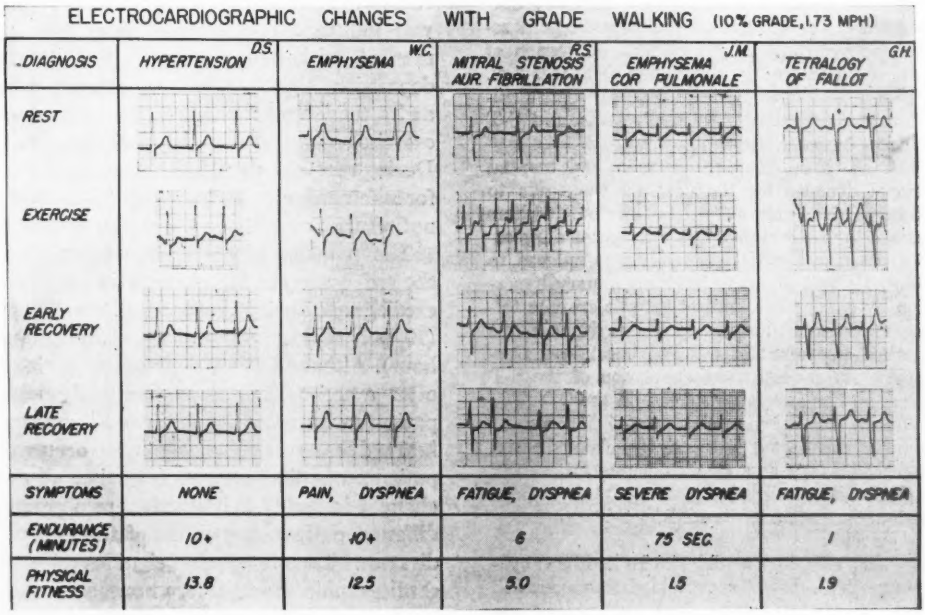

FIG. 4

FIGS. 3 and 4. These two graphs show illustrative electrocardiographic tracings during rest, exercise, and recovery in 9 patients with various cardiopulmonary diseases. The description of changes is in the test.

(5) D. S. This 52 year old biophysicist had an exercise tolerance test in order to evaluate his physical condition. He had had no symptoms. The only positive physical finding was a slightly high blood pressure, which was 160/118 at rest. Exercise tolerance test for 10 minutes showed some lowering of the T wave in the electrocardiogram during exercise. This was considered to be due to tachycardia, and not significant of disease.

(6) W. C. This 61 year old man complained of exertional dyspnea, and cramps in the calves of his legs for the past three years. He had physical signs of emphysema, confirmed by a grossly increased residual air volume amounting to 56 per cent of the total pulmonary capacity. Although he experienced some pain and dyspnea, he was able to walk for 10 minutes. His chest lead electrocardiogram showed a normal response. There was no evidence of coronary insufficiency in this patient, despite pain and dyspnea on exertion.

(7) R. S. This 36 year old man had an attack of subacute bacterial endocarditis complicating mitral stenosis, in February, 1950, which was treated well with penicillin. Physical examination and fluoroscopy of the chest in March, 1950 showed marked enlargement of the heart, signs of mitral stenosis and auricular fibrillation. He was able to walk for only 6.2 minutes because of excessive fatigue and dyspnea. There was marked hyperventilation with a paradoxic response of respiratory efficiency during exercise. The chest lead electrocardiogram revealed tachycardia and considerable depression of the S-T segment during exercise and early recovery. In common with other patients with auricular fibrillation, there was a marked tachycardia and S-T depression during exercise.[5]

(8) J. M. This 62 year old man had marked exertional dyspnea for the past six years due to emphysema. The residual air volume of 3.6 liters amounted to 64 per cent of the total pulmonary capacity, whereas the vital capacity was reduced to 0.6 liter. He was found to have pulmonary hypertension by cardiac catheterization. His exercise tolerance was grossly impaired by severe dyspnea due to marked hyperventilation. The chest lead electrocardiogram showed some depression of the S-T junction, and an abnormal increase in the Q-T:T-Q ratio during the exertion. He was slightly helped by digitalization, and subjectively claimed even greater benefit from an artificial pneumoperitoneum. The chest lead electrocardiogram of this patient showed accentuation of the slight S-T depression during exercise.

(9) G. H. This 20 year old woman had been cyanotic since birth, showed some retardation of growth and had frequent infections. In recent years there had been appreciable spontaneous improvement in exercise tolerance, whereas in childhood the patient frequently squatted. Physical examination showed marked clubbing, polycythemia, cardiac enlargement, accentuation of second pulmonic sound, a systolic murmur and thrill as well as decrescendo diastolic murmur along left sternal border. Exercise tolerance was markedly impaired because of fatigue, dyspnea, and tachycardia. There was a slight elevation of the T waves in the chest lead electrocardiogram. Exploratory thoracotomy revealed abnormal pulmonary artery, features compatible with tetralogy of Fallot, as well as too many collaterals to warrant attempting further dissections necessary for an artificial anastomosis. Again, the earliest evidence of coronary insufficiency was suggested by the increased voltage of the T waves.

Discussion

The data presented herein was based upon grade walking on a treadmill ergometer at 1.73 miles per hour. This was considered to be a more satisfactory standard exercise test than level walking.[2] In normal controls the precordial lead electrocardiograms showed responses similar to those in normal subjects with level walking.[1]

This report shows that definite changes in the electrocardiograms occurred in normal subjects when the work load was increased further, or when moderate or severe hypoxia was induced. The changes were even more marked with both stresses. Definite RS-T depression, high Q-T:T-Q ratio during exercise and a tendency for the $Q\text{-}T_c$ to decline during exercise were the most constant findings. During recovery the RS-T depression persisted for a few minutes and the Q-T:T-Q ratio did not return promptly to the resting value.

The patients with acquired heart diseases showed quite similar changes in the electrocardiograms during the standard exercise stress (10 per cent grade walking, 1.73 miles per hour). Although RS-T depressions during and after exercise were most frequently seen in patients with arteriosclerotic and hypertensive heart diseases, this change also occurred in patients of other groups. Likewise, abnormal changes in the Q-T interval were observed in different patients regardless of the underlying diseases. Therefore, the significant electrocardiographic changes were nonspecific for any particular group of patients. Since the electrocardiographic changes in either normal subjects under unusual stresses or in patients with disease were indistinguishable from each other,

it was difficult to differentiate "functional" from "organic" coronary insufficiency. Possibly the use of dihydroergocornine would aid in this differentiation.[5]

The close relationship between the Q-T:T-Q ratio and the presence of precordial pain has been discussed previously.[1] It was suggested that excessive shortening of the duration of diastolic filling (when the Q-T:T-Q ratio was high) might impede the coronary blood flow, especially in patients with arteriosclerotic changes of the coronary arteries. Whereas no normal subjects experienced precordial pain even when the Q-T:T-Q ratio exceeded 2.5 and marked RS-T depression occurred, patients with arteriosclerotic and hypertensive heart diseases frequently complained of precordial pain. There was some evidence in normal subjects under unusual stresses that there may be a redistribution of blood during exercise to spare the vital organs such as the heart.[3]

The $Q\text{-}T_c$ pattern in the congenital heart group was rather unique in that it showed reduction during exercise and increase during early recovery. This was more striking in those cases with cyanosis. So far patients with coarctation of the aorta have been exceptions to this. More cases of congenital heart disease need to be studied, however. Patients with compensated rheumatic heart diseases usually show a normal response in the $Q\text{-}T_c$. Hence this may aid differential diagnosis between these two groups of patients.

The mechanism of the depression of RS-T segment is probably due to injury of the subendocardial layers of the myocardium as a result of reduced coronary blood flow, or anoxia. Recently it was demonstrated conclusively by experimental studies[7, 8] and clinical observations[9, 10] that the essential change in the electrocardiograms in subendocardial myocardial infarction is a marked RS-T depression in the left precordial leads. The presence of high T wave has also been shown experimentally to be a result of early injury of subendocardial layer[11] and clinically, an early sign of myocardial infarction.[12] The appearance of a high, peaked T wave during exercise is of particular interest, because it may indicate an early abnormal response that has not been emphasized before. One of the patients in the group with arteriosclerotic and hypertensive heart disease showed a distinct increase in the T wave during exercise, and 10 days later he developed coronary occlusion. Scherf[13] has stated that "damage of the inner layers of the myocardium causes depression of the RS-T segment and the T wave as an acute effect and high-positive T waves as an after-effect." Our experience has led us to believe that the appearance of high peaked T wave is probably an acute effect. Should electrocardiogram be taken routinely *during* exercise, a higher incidence of the high T waves might be observed.

The conspicuous advantages of registering a precordial lead electrocardiogram with a direct writing instrument during treadmill walking can not be overemphasized. A similar study has been applied to the performance of the Master two step test; the results have been uniform and encouraging.[14] First, the recording of the chest lead is superior to that of standard leads because marked changes may appear in the former and be absent in the latter.[15] Second, important changes in the electrocardiograms may appear only during exercise, and disappear as soon as the exercise has been discontinued, or within two or three minutes.[13] These include reduction of the R wave and increase in the QS wave, significant increase in the voltage of the T wave, marked depression in the RS-T segment and multiple ventricular premature beats. Finally the measurement of the Q-T interval as a quantitative measure to differentiate normal from abnormal responses has been found to be helpful in majority of the cases. In normal subjects performing the standard exercise test the patterns of response in both $Q\text{-}T_c$ and Q-T:T-Q ratio have been described. In patients with various types of cardiopulmonary diseases, the incidence of abnormal responses was quite high. The percentage of abnormal response was even greater in patients with marked disability than in those with no or moderate disability. In some patients there was no alteration of the RS-T segment and T wave, yet the response in Q-T pattern was distinctly abnormal.

SUMMARY

1. Walking on a treadmill at a pace of 1.73 miles per hour and 10 per cent grade has been adapted in this laboratory as a standard exercise test. Minute-by-minute chest lead electrocardiograms were recorded, before, during, and after the exercise. The electrocardiographic response in 20 normal subjects was similar to that observed in level walking, which has been previously described. The criteria of the abnormal responses in the standard test in regard to changes in the Q-T pattern, RS-T and T waves and premature beats have been defined.

2. Abnormal electrocardiographic changes are described in a group of 7 normal subjects walking on the treadmill with increased work load or induced hypoxemia or both. The magnitude of these changes was directly proportional to the severity of the stresses.

3. Standard exercise tests were also performed in a group of 48 patients with various kinds of cardiopulmonary diseases. The electrocardiographic changes obtained from these patients have been analyzed and compared with those of the 20 normal controls. It was found that about two-thirds of the patients showed an abnormal response. The incidence of abnormal electrocardiographic changes varied inversely with the duration of exercise.

4. The electrocardiographic abnormalities in both normal subjects under unusual stresses and patients with cardiopulmonary diseases were comparable. The changes in either group were considered as significant but nonspecific.

5. The advantages of registering chest lead electrocardiograms *during* exercise have been discussed.

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Determinants of Impairment of Cardiac Filling During Progressive Pericardial Effusion

By WILLIAM E. NERLICH, M.D.

The progressive reduction in cardiac output—and later in arterial pressures—that develops during advancing degrees of pericardial effusion is usually attributed to a steady decrease in the venoatrial pressure gradient. Evaluation of changes in instantaneous pressures in the right and left atria at the end of ventricular diastole (Z pressure) and systole (V pressure) indicates that as pericardial pressure rises other determinants enter in the following order: (1) reduction in diastolic capacities of the atriums and ventricles; (2) decrease in venoatrial pressure gradient and preponderant rise of left atrial pressures due to the higher elasticity coefficient of this chamber; (3) blockage of atrial inflow during ventricular diastole; (4) impairment of atrial inflow during ventricular systole as its stroke volume diminishes to an extreme degree; and (5) inauguration of a vicious cycle in which a diminishing venopressure gradient decreases ventricular filling, while the consequent reduction in stroke volume attenuates the facilitating effect of ventricular ejection on the venoatrial gradient.

SINCE THE initial work of Cohnheim,[1] it has been known that the rapid introduction of fluid into the pericardial sac of experimental animals produces an increase of venous pressure and a fall of mean arterial pressure. The data later collected by Starling,[2] Lewis,[3] Kuno,[4] and others demonstrated that the increased pericardial pressure acts as a barrier to the venous filling of the heart, resulting in a decrease in diastolic heart size when the gradient of pressure between the central veins and atrium is sufficiently diminished. The rise of central venous pressure results from pooling of venous blood which has failed to reach the right atrium, and the fall of mean arterial blood pressure is ascribed to the progressively decreasing cardiac output.

It was the purpose of this investigation to subject the accepted dynamics of pericardial effusion to closer scrutiny and, if possible, to evaluate the importance and incidence of other suspected and unsuspected determinants of reduced ventricular filling and output. Incidentally, it seemed important to determine whether the right and left sides of the heart react similarly and simultaneously to a common increase in pericardial pressure. For these purposes, right and left atrial and pericardial pressures were recorded by optical manometers during stepwise increases in pericardial fluid. "Open chest" preparations were employed so that the complicating effects of changing intrathoracic pressure would not be involved in the analysis of basic hemodynamic effects.

METHODS

After the animals had been anesthetized with morphine and phenobarbital sodium, artificial respiration was given and the chest was opened through a midline sternum-splitting incision. Cannulas filled with saline and heparin were inserted (1) into the left atrium via the superior branch of the left pulmonary vein, (2) into the right atrium via the right jugular vein, and (3) into the aorta via the left subclavian artery. A cannula filled with saline was also inserted into the ventral surface of the pericardium without disturbing the pericardial diaphragmatic attachments or introducing air. The cannula was adjusted so as to cause minimal distortion of the pericardial sac and to avoid impacts of the contracting ventricles.

The various cannulas, rigidly fixed, were attached by lead tubing to Gregg-type manometers of adequate sensitivity and frequency for the optical registration of each pressure curve. The level of the animal board was used as a zero for all manometers. Changes in atrial levels such as are caused by lung inflation and deflation were controlled by recording

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these acts on the same record by means of a Frank segment capsule connected with the outlet tube of the respirator. The atrial and pericardial manometers were calibrated against a saline manometer, the aortic manometer against a mercury manometer. Pressure relations to a base line were checked after each record. After placement of cannulas was such that good records resulted, the cannulas were maintained in a fixed position and were not manipulated during the experiment, a point of considerable importance.

After the animal's blood pressure had stabilized, as evidenced in a series of control records, isotonic saline at 38 to 50 C. was introduced into the pericardium in 5 or 10 cc. increments at intervals of four minutes until the arterial pressure and/or heart rate had declined to precarious levels. After a short period of stabilization in this dynamic state, the pericardial fluid was slowly withdrawn in 5 cc. increments. Optical records were taken after each alteration in pericardial volume throughout the experiment.

Measurement of Atrial Pressure Curves. It has been stressed in several communications from this laboratory[5–7] that measurements of instantaneous atrial pressures at definitive moments of the cardiac cycle are superior to mean pressure values in interpretations of dynamic problems. Accordingly, all measurements were made at the Z point, which expresses the state of atrial pressures at the onset of ventricular systole, and at the V point (at the moment of the second heart sound) which occurs at the end of venticular systole. These points are marked on record C of figure 1. Since pericardial pressures also fluctuate during the cardiac cycle as soon as a layer of fluid surrounds the ventricles, pericardial pressures were measured at corresponding points.

Results

Fifteen experiments were performed but the data of only nine were considered sufficiently reliable to be included in this survey; the others were vitiated by the necessity of changing the position of recording cannulas or by the development of leaks in the pericardial sac.

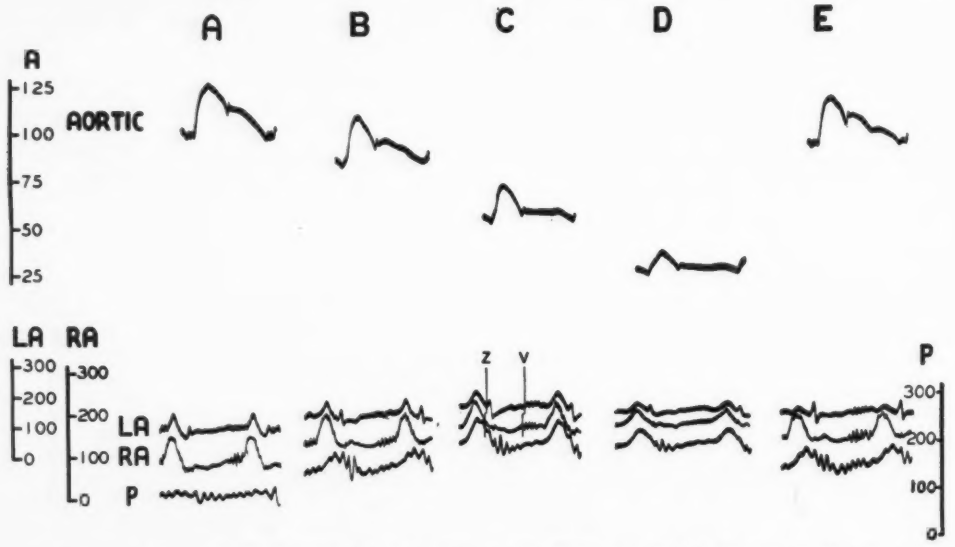


Fig. 1. Pressure pulses in aorta, left atrium (L. A.), right atrium (R.A.), and pericardial cavity (P). *A*, control; *B*, during phase I of pericardial infusion; *C*, during phase II; *D*, during phase III; *E*, after removal of pericardial fluid. Discussion in text. Calibration curves in mm. Hg for aortic curves; in mm. H_2O for other curves.

Actual pressure changes in the aorta, left atrium, right atrium, and pericardium during different stages of experimental pericardial effusion are shown in segments *A*, *B*, *C*, and *D* of figure 1. The effects of complete recovery are shown in segment *E* of the same figure. Figure 2 shows plots of data derived from similar curves in another experiment.

On the basis of trends in mean arterial pressure, the sequence of dynamic events following progressive increase and decrease in volumes of

pericardial fluid can be divided into four stages. These are indicated in the plot of figure 2.

Phase I starts with the introduction of saline solution into the pericardial sac and continues until approximately two-thirds of the maximal volume which can be introduced has been introduced. It continues as long as mean arterial pressure remains at the control level or declines only slowly. Frequently, as in the experiment plotted in figure 2—but not necessarily as shown in segment *B* of figure 1—the heart accelerates progressively. The reduction in diastolic size which accompanies such acceleration aids the heart in adapting its capacity to the diminishing pericardial space. The period of systolic ejection becomes shorter, even when the heart rate remains relatively constant, as in figure 1*B* and *C*. The pulse pressure diminishes and the contour of the pressure pulse (fig. 1*B*) shows a significant reduction in stroke volume. In fact, estimates of stroke volume and cardiac output by the pulse contour method of Hamilton and Remington, shown in the third curve of figure 2, indicate that cardiac output is diminishing steadily. The mechanism by which arterial pressure is sustained can be only inferred from the data, but an increase in total peripheral resistance was demonstrated in similar experiments by Post.[8]

Phase II is characterized by the precipitous decline of arterial pressure which follows additional small increments of pericardial fluid. Often, as in the experiment illustrated in figure 1, the heart slows abruptly to a rate well below normal. As shown in figure 1*C*, the pulse pressure diminishes progressively and the pressure pulse assumes a rounded configuration and flattened diastolic limb. Analyses by the pulse contour method indicate a continuing reduction in stroke volume and, owing to a pronounced slowing, a still greater decrease in cardiac output.

Phase III represents the interval during which arterial pressures reach a critically low level; indeed, small volumes of pericardial fluid may need to be withdrawn in order to maintain a barely minimal circulation. Ordinarily, the heart rate and arterial pressures are lowest during this period. The pulse pressure is small and, as seen in figure 1*D*, the contour of the aortic pressure pulse suggests a very small output.

Phase IV comprises the steady recovery of arterial pressure and heart rate following stepwise removal of pericardial fluid. The circulatory changes are essentially the reverse of those seen during addition of fluid; the heart promptly regains its control rate and the mean arterial pressure its control level, but the pulse

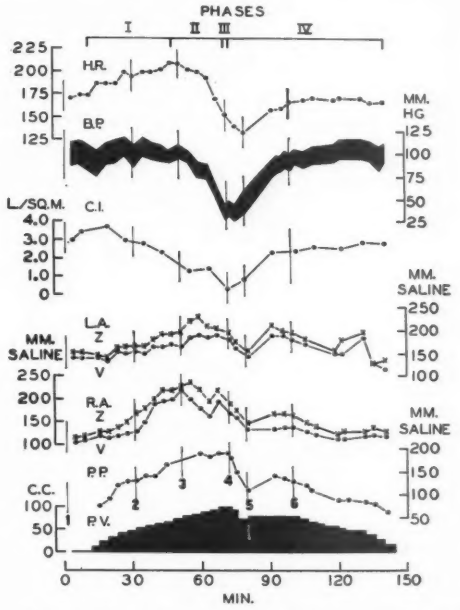


FIG. 2. Chart showing effects of increasing and decreasing pericardial fluid volumes (P.V.) on heart rate (H.R.), systolic and diastolic pressures (B.P.); cardiac index by pulse contour method (C.I.); Z and V pressures in left atrium (L.A.), and right atrium (R.A.), and in pericardial cavity (P.P.). I, II, III, IV indicate sequential phases discussed in text; 1, 2, 3, 4, 5, 6 indicate coordinate cross lines interrelating different curves.

pressure and cardiac output are not quite restored to normal.

A glance at the lower group of pressure curves in figure 1 clearly shows that the general level of both right and left atrial pressures elevates with that of the pericardium. It is also noticeable that whereas the pressure curves from the pericardial sac exhibit only random vibrations when no fluid is present (*A*), the curves assume more and more the form of changes within the atrium as fluid accumulates.

The surprising feature of such records is the small reduction in pressure that occurs when the massive ventricles empty during systole and the relatively large pressure wave that accompanies atrial contractions (fig. 1*B* and *C*). This stresses the fact that, in studying the effect of increasing pericardial pressure, we need to consider two oppositely directed forces, namely, the reciprocal effects of increasing pericardial upon atrial pressures and the dynamic effects of intraatrial pressure changes upon phasic pericardial variations. To judge from the amplitudes of the conspicuous atrial waves in records such as these, increased pericardial pressure does not seem to diminish the vigor of atrial contractions until the third phase is approached (*D*). However, it is impossible to exclude a depressant vagal effect on atrial contraction coincident with the slowing, for the vagus exerts similar effects on atrial pressure curves.[9]

Careful measurements of atrial pressure curves are required to determine the relative effects of increasing pericardial pressure on the instantaneous Z and V pressures in the two atria, and caution is required in their interpretation. As analyzed by Opdyke and his associates,[6] under natural conditions the instantaneous Z and V pressures allow inferences regarding inflow-outflow equilibria in the atriums at the ends of diastole and systole respectively. During varying degrees of pericardial tamponade such interpretations must be tempered by the reciprocal reactions between pericardial and intraatrial pressures. Nevertheless, gross differences in the trends of Z or V pressures in the two atriums become significant since they are subject to identical pericardial pressures.

In the chart of figure 2, it is observed that the initial increase in pericardial pressure (PP), caused by injection of five 10 cc. units of saline (PV), has only slight effect on the Z and V pressures (lines 1 and 2). The Z pressure in the right atrium rises first and to a greater extent than in the left; but in some other experiments the Z pressures increased in both atria. Such precedent elevation of Z pressure—at the end of ventricular diastole—is understandable, for increasing volumes of pericardial fluid will tend to restrict the diastolic but not the systolic size of the heart. Wiggers[9] also found that pericardial volumes of similar magnitude cause a recognizable elevation of initial tension in the left ventricle which corresponds to Z pressure in the left atrium. Such precedence in elevation of Z pressure allows the inferences (a) that these pressures give an idea of the extent to which pericardial fluid encroaches upon the capacity of the atria, and (b) that the primary decrease in cardiac output is due to the reduced diastolic capacities of the atria and ventricles.

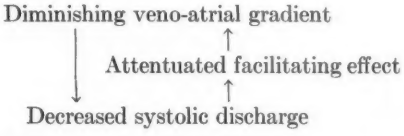
The introduction of additional 10 cc. of increments of saline solution has a different effect on atrial pressures (lines 2 and 3). Right atrial V pressure now increases steadily, while left atrial V pressure is elevated only slightly. Since the steadily rising pericardial pressure acts equally at the two atriums, and since the accompanying acceleration of the heart in this experiment would in itself tend to lower both atrial V pressures, the possibility must be considered that the systolic inflow into the left atrium is reduced relatively more than that of the right. The following reasoning could be applied. The progressive reduction of pulse pressure and cardiac output obviously denotes impairment of left ventricular filling. This is now due to diminishing capacity of the left heart plus a diminishing pressure gradient between the pulmonary veins and the left atrium. Since filling and output of the right heart are simultaneously reduced the pressure in the pulmonary veins never rises as much as in the venae cavae. For this reason the right atrial pressure at the end of systole (V pressure) rises earlier, more rapidly, and to a higher level than the V pressure in the left atrium. In other words, the pressure in the systemic venous reservoir is more effective for maintaining atrial filling than that in the pulmonary venous reservoir, because the latter depends on the diminishing output of the right ventricle. Such an interpretation is weakened by the fact that under such conditions inequality of the stroke volumes of the two ventricles must exist for some time and such disparity between the minute outputs of the two ventricles, even for a few beats, would cause an elevation of pulmonary venous pressure perhaps equal to that in the systemic venous reservoir.

The different effects of rising pericardial pressures on the V and Z pressures are more probably related to the higher elasticity coefficient of the left atrium.[10] Thus, assuming as a first approximation that the elasticity coefficients $\left(\frac{dp}{dv}\right)$ of the respective atriums do not change as pericardial pressure rises, it can be postulated that the pressure at the end of systole (V pressure) is determined by *net systolic inflow* $\times \frac{dp}{dv}$ + *pericardial pressure*. By giving $\frac{dp}{dv}$ for the left atrium any larger value than that for the right, a little calculation reveals that right atrial V pressure rises faster than left atrial pressure with equally diminishing inflow volumes. An example is shown in table 1. Similarly, the more rapid elevation of right atrial Z pressure can be explained if the inflow figures assumed in this table are taken to indicate inflow during the entire heart cycle.

TABLE 1

Left Atrium					Right Atrium				
Inflow	×	$\frac{dp}{dv}$	+ Pericard. Press.	= V or Z Press.	Inflow	×	$\frac{dp}{dv}$	+ Pericard. Press.	= V or Z Press.
10		4	0	40	10		2	0	20
8		4	10	42	8		2	10	26
6		4	20	44	6		2	20	32
4		4	30	46	4		2	30	38
2		4	40	48	2		2	40	44

The possible determinants of atrial V and Z pressures so far discussed are not the only ones concerned, for, as shown between lines 3 and 4 of figure 2, further increase in pericardial volume and pressure reverses the trends of V pressures; they now decline somewhat in the right atrium and rise in the left. The Z pressures also follow in the right atrium but start to decline in the left. Any attempt to analyze these confusing directional changes becomes hazardous because many conflicting factors are introduced at this time. The heart slows progressively and arterial pressure begins its abrupt decline, while the capacities of the atria and ventricles are further reduced by the rising pericardial pressure. The net effect of these forces is a progressive reduction in stroke volumes to very low levels, despite the prolongation of the filling period incident to cardiac slowing. This slowing is at least partly of cardiac origin, for it persists after vagotomy.[9] A study of pressure pulses during this period suggests that atrial inflow may be blocked during diastole and occurs solely during ventricular systole. As shown in figure 1*C*, systolic emptying of the ventricles causes a significant reduction in pericardial pressure, which aids the diminishing venoatrial pressure difference to fill the atrial chambers during systole. This facilitating hemodynamic force is greatly attenuated as pericardial pressures reach still higher levels (lines 4 and 5, fig. 2), for, with further impairment of ventricular filling, ventricular contractions reduce pericardial pressures very little, as illustrated in figure 1*D*. Thus, a vicious cycle is established which eventuates in a pronounced reduction of cardiac output and a decline of arterial pressures to critically low levels (fig. 2, line 4). This may be expressed diagrammatically as follows:



In summary, development of the critical stage of pericardial effusion is hastened by the reciprocating effects of diminishing venoatrial pressure differentials on ventricular filling, and the progressive attentuation of the facilitating effect that contraction of the ventricles exerts on atrial inflow through systolic reduction in pericardial pressure.

The question of whether reduction in coronary flow contributes to the default of ventricular contraction must be left unanswered.

The writer has found no experimental studies of the problem, and Gregg mentions no such work in his recent monograph.[11] Electrocardiographic studies cannot differentiate between myocardial effects caused by ischemia and those produced by other agencies. The volume of coronary flow during states of high pericardial pressure would be the result of many factors, among them lowering of arterial pressure, the elevation of diastolic and reduction of systolic pressures

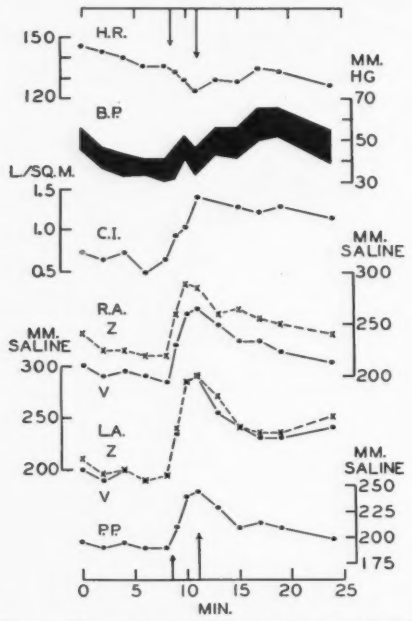


FIG. 3. Plot of dynamic events showing the effect of 100 cc. intravenous saline solution during period indicated by arrows, on hemodynamic events. Symbols as in figure 2. Discussion in text.

within the ventricles, the extracardial tension and uncertain effects of anoxia and metabolites on the tone of intramural arterioles. Speculation as to resultant effects on coronary flow and its adequacy for the reduced work and abnormal mode of performance is obviously hazardous. That any such effect was not lasting in these acute experiments is indicated by the observation that removal of only a small volume of pericardial fluid promptly improves cardiac action. In the experiment illustrated in figure 2, removal of 30 cc. of saline (lines 4 and 5) reveals a significant reduction in pericardial and atrial pressures but no marked immediate effect on cardiac output or arterial pressure. Gradually (lines 5 and 6) a recovery of cardiac output, arterial pressures, and the heart rate occurs which corresponds rather well with conditions when similar pericardial volumes existed during introduction of saline (cf. curves at lines 3 and 6). The greater reduction of pericardial pressure at apparently equivalent volumes (lines 3 and 6) may have been due to (a) stretching of the plastic pericardium or (b) absorption of some of the saline solution. The presence of leaks was meticulously excluded. Similar factors may account for the common observation illustrated in figure 1*C* and *D*, that pericardial pressures often decline when excessive volumes of fluid are introduced.

The rate at which cardiac output decreases with progressive elevation of pericardial pressure depends upon the volume of circulating blood and the magnitude of the pressure elevation that can take place in extrapericardial veins. To determine the importance of this factor, two animals with extremely large pericardial effusions were given intravenous infusions of 100 cc. saline solution over a period of four or five minutes. The effects were rather surprising, as indicated by data of one experiment in figure 3. It can be easily seen that such an infusion induces a prompt elevation of Z and V pressures in both atriums. As in normal dogs (Opdyke), these pressures rose higher in the left than those in the right atrium. The abrupt increase in cardiac output is evidence that a marked improvement in cardiac filling had taken place and that this occurred despite a further rise of pericardial pressure—probably as a result of the greater filling of the heart. The most interesting feature, however, was the fact that the effects of such a temporary infusion extend far beyond the period of infusion. As shown in figure 3, intraatrial Z and V pressures decline shortly after termination of the infusion, but they are maintained at a much higher level than before the infusion. The initial improvement in cardiac output is also maintained; arterial pressures remain higher and the pulse pressures larger. More favorable venoatrial gradients are obviously responsible for the improvement. The fact that the Z pressure equals or exceeds the V

pressure in the atria supports the view that atrial inflow takes place throughout the cardiac cycle.

Summary and Conclusions

An experimental attempt was made to evaluate the dynamic factors that operate to reduce cardiac output during progressive stages of pericardial effusion and to determine whether the right and left hearts are affected similarly and simultaneously when submitted to a common increase in pericardial pressure. For this purpose, a special study was made of the changes in instantaneous atrial pressures measured at the end of diastole (Z pressure) and at the termination of systole (V pressure). The contemplated analysis failed to identify the dominant factors at certain stages of pericardial tamponade, but they proved informative in the following ways:

1. The characteristic precedent elevation of Z pressure, particularly in the right atrium, strongly suggests that reduction in diastolic capacities of the atria and ventricles is the first factor that reduces systolic discharge.

2. The steady rise of right atrial V pressure and the small rise of left atrial V pressure following the progressive increase in pericardial fluid suggests that the venoatrial pressure gradient diminishes more rapidly on the left side. Such an interpretation is untenable, however, since it involves a disparity between the outputs of the two ventricles, a condition that cannot be maintained for more than a few beats. The higher elasticity coefficient of the left atrium seems to account for these differences.

3. During the phase when arterial pressures decline abruptly, other determinants enter, but their nature cannot be detected by analysis of atrial pressure pulses.

4. A study of pericardial pulsations reveals that the reduction in pericardial pressure during ventricular ejection facilitates atrial filling by creating a more favorable venoatrial pressure gradient. It is probable that with increasing pericardial pressures atrial inflow is blocked, first during the period of ventricular diastole and only later during the period of ventricular systole.

5. It is believed that development of the critical stage is hastened through establishment of a vicious cycle: diminishing venoatrial gradient → decreased systolic discharge → attenuated facilitation effect of ventricular systole → further reduction of venoatrial gradient and repetition of the cycle.

Acknowledgments

The author wishes to acknowledge his indebtedness to Drs. R. S. Alexander, D. F. Opdyke and C. J. Wiggers, for their critical help in evaluating the results and their assistance in the preparation of this manuscript.

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The Isolation of Hypertensin from the Circulating Blood of Normal Dogs with Experimental Renal Hypertension by Dialysis in an Artificial Kidney

By LEONARD T. SKEGGS, PHD., JOSEPH R. KAHN, M.D., AND NORMAN P. SHUMWAY, M.D.

Hypertensin has been dialyzed out of the circulating blood of dogs by means of an artificial kidney and a new method has been devised for its recovery from the dialyzate. More hypertensin was recovered from the dialyzate obtained from dogs with experimental renal hypertension than from normal animals.

THE PRESENT paper is a report on experimental procedures designed to determine whether hypertensin is the vasoconstrictor substance responsible for the elevation of blood pressure in dogs with benign experimental renal hypertension. Previous work[1] has shown that a pressor material similar in all general respects to hypertensin can be dialyzed out of the circulating blood of dogs by the use of an artificial kidney.[2] The pressor material was present in the dialyzates of dogs under the following experimental conditions: (1) 4 dogs with malignant hypertension; (2) 2 out of 9 normal animals; (3) 2 normal dogs in which the artificial kidney was filled with blood from donor dogs which were not nephrectomized; and (4) 3 out of 9 dogs which were injected intravenously with varying amounts of renin. The dialyzates from the dogs were worked up chemically and then injected intravenously into rats to determine the amount and kind of pressor material that was present. The rat was chosen as the test animal because it was found that 0.01 of a Goldblatt unit of hypertensin[3] gave a rise of 20 to 30 mm. Hg in the blood pressure of the anesthetized animal. The rise in blood pressure produced in the rats by the injection of the pressor material recovered from the dialyzates was compared to the rise following the administration of 0.01 unit of hypertensin. In both instances it was found that the maximum rise in blood pressure occurred in one minute or less and returned to normal in three minutes or less. The pressor material recovered from the dialyzates was destroyed by incubation with hypertensinase, crystalline trypsin and pepsin. Pharmacologic studies revealed that the pressor material did not produce tachyphylaxis, nor was the pressor effect changed by previous injections of cocaine, atropine or 933 F; however the pressor response was potentiated by a previous injection of tetraethylammonium chloride. The material was destroyed by boiling at a pH of 12 but not at a neutral pH or at a pH of 1. The pressor substance was slowly dialyzable through a cellophane membrane, was water and alcohol soluble and ether insoluble. Thus this pressor material was found to have the general properties of hypertensin.[4]

The loss of pressor material which occurred during the chemical preparations of the dialyzates in these experiments was so great that no reliable quantitative results could be obtained. The experiments showed only qualitatively that hypertensin was present in the circulating blood of the dogs with malignant hypertension as well as in an occasional normal dog.

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It was necessary, therefore, to develop a new method for recovering hypertensin from the dialyzate which would give a more consistent and better yield. The method described in this paper gave a 50 to 80 per cent recovery of hypertensin from the dialyzate.

Experimental Procedures

The same experimental procedures were used for the dialyses in these experiments as in our previous work. In brief these methods were as follows. Dogs were used in all experiments and received 15 mg. of morphine sulfate and 0.4 mg. of atropine sulfate 15 to 30 minutes before the experiments were started. The artificial kidney was connected to the femoral artery and femoral vein by means of rubber tubing. The pressure in the femoral artery produced a blood flow of 100 to 200 ml. per minute through the kidney. The experimental animals were dialyzed for two consecutive 90 minute periods against 500 ml. of circulating dialyzing solution which usually increased by 100 ml. to 200 ml. by ultrafiltration in each 90 minute period. The composition of the dialyzing solution was Na^+ 148, Ca^{++} 5, K^+ 3, Mg^{++} 3, Cl^- 126, HCO_3^- 24, HPO_4^{--} 2, and lactate$^-$7, mEq. per liter plus 100 mg. of glucose per 100 ml. The pH of the solution was 7.35 to 7.45. At the end of each 90 minute period, the dialyzate was collected, cooled in ice to 3 C. and stored in the deep freeze until chemical processing could be undertaken.

All of the dogs were heparinized, receiving at the beginning of the experiment 4 mg. per Kg. of heparin and throughout the experiment 0.5 mg. per Kg. per hour.

The dialyzing solution was pumped through the kidney by means of a Sigmamotor pump, at a rate of 200 ml. per minute and at a negative pressure of 10 mm. Hg. The dialyzate passed through a copper coil placed in a water bath which was maintained at 39 C. This was found to maintain the temperature of the blood circulating through the kidney at 38.5 C. A needle attached to a mercury manometer was inserted into the rubber tubing which connected the femoral artery with the kidney, so that the approximate mean blood pressure of the animal could be observed throughout the experiment.

Four hundred ml. of blood collected from donor dogs by arterial puncture into a flask which contained 20 mg. of heparin and 20 ml. of normal saline. This blood was used to fill the artificial kidney and the rubber tubing which connected it to the experimental animal. The artificial kidney, the rubber tubing, and the air trap held 250 ml. of blood; 50 ml. were discarded and the remaining 150 ml. of blood were given by slow intravenous drip throughout the early period of the dialysis. The pressure of the blood in the kidney was raised by adding blood to it with a syringe until it was equal to the arterial pressure of the dog to be dialyzed. By this procedure, there was no loss of blood or fall in the blood pressure when the dialysis was started. All of the donor dogs were bilaterally nephrectomized for at least 18 hours before they were bled and some as long as 96 hours. Nephrectomized donor dogs were used in order to make sure that the hypertensin recovered in the dialyzate came from the animals that were being dialyzed, and not from the donor dogs.

The following methods were used in preparing the dialyzates for intravenous injections into rats. The dialyzate was removed from the deep freeze, thawed in warm water and processed in 300 ml. quantities. Each 300 ml. was subjected to the following procedures. The pH of the solution was immediately adjusted to 3 ± 0.1 by the addition of 8 to 10 ml. of 1 N hydrochloric acid and then was vacuum concentrated to 10 ml. in a one liter round bottom flask at temperatures below 20 C. Twenty-five ml. of redistilled *n*-butanol was added, the flask was stoppered, shaken for five minutes, transferred to a 50 ml. centrifuge tube and then centrifuged for two to three minutes in order to break the emulsion. The butanol layer was transferred to a 250 ml. Erlenmeyer flask. The one liter flask used for evaporation was washed with 25 ml. more of butanol decanted into the centrifuge tube containing the original water layer, stoppered, shaken for five minutes, centrifuged and the second butanol layer was combined with the first one in the Erlenmeyer flask. The hypertensin was now dissolved in the butanol while most of the salts remained in the water. The hypertensin was removed from the butanol by adsorption on to 5 Gm. of alumina which was added to the Erlenmeyer flask and agitated for five minutes.

The alumina[5] (activated 80 to 200 mesh Fisher Scientific Co.) was prepared in the following fashion: 600 Gm. of alumina were shaken intermittently for one hour with 3 liters of concentrated hydrochloric acid diluted 1:5 with distilled water. The hydrochloric acid was filtered off, the alumina was washed thoroughly with distilled water (about 30 gallons) until the wash water, when treated with silver nitrate, gave only a faint opalescence. The alumina was then air dried for 48 hours.

The butanol with the suspended alumina was poured into a 50 ml. medium porosity sintered glass funnel, fitted for vacuum filtration. The butanol was filtered off, discarded and 40 ml. of 90 per cent ethanol were added to the alumina, stirred for one minute, and then filtered off. The alcohol wash was repeated once more and the ethanol washes were discarded. The hypertensin was removed from the alumina by washing it twice with two 40 ml. quantities of distilled water which were stirred each time with the alumina for five minutes. The water with

the dissolved hypertensin was then filtered off the alumina and poured into a beaker containing 4 Gm. of Amberlite (IR-4-B Rohm & Haas). The Amberlite was prepared for use in the following manner: 200 Gm. of Amberlite were washed thoroughly with running distilled water until the wash water showed no opalescence with phosphotungstic acid. The Amberlite and water containing the dissolved hypertensin were stirred until the pH had risen to 6.1 ± 0.1. The resin was filtered off immediately and discarded. The filtrate containing the hypertensin was concentrated under a vacuum in a 500 ml. round bottom flask to approximately 3 ml., and then transferred to a 15 ml. centrifuge tube with the aid of small washes of distilled water. A drop of phenol red indicator was added and the pH adjusted to approximately 7.0 by the addition of either 0.1 N hydrochloric acid or sodium hydroxide solutions. The solution was centrifuged at high speeds to remove small amounts of insoluble materials. The clear supernatant fluid was transferred to a 10 ml. ampoule, shell frozen and then lyophilized. Following lyophilization, the ampoule was sealed and stored at room temperatures until it could be assayed for its content of hypertensin. At the time of the assay, the material was dissolved in either 0.5 or 1.0 ml. of distilled water.

Assays of the dialyzates were performed on mature rats anesthetized with Sodium Amytal, 9 mg. per 100 Gm. of body weight injected intraperitoneally. Atropine, 0.4 mg., was administered intraperitoneally at the same time the Amytal was given. Thirty minutes after the administration of the anesthetic, both vagus nerves were cut and the trachea was cannulated. A needle was inserted and tied into the left jugular vein; this was used for intravenous injection of the material that was to be assayed. The right carotid artery was cannulated and connected with a capillary mercury manometer equipped with a pen for ink writing on a kymograph.

All of the tests on the dialyzates were done with small volumes ranging between 0.25 and 0.50 ml. The rises in the rats' blood pressure were compared with those obtained by the injection of 0.01 unit of hypertensin prepared from standard lyophilized powder. One unit of this standard gave an average rise in blood pressure of 32 mm. Hg in 12 nembutalized rabbits and an average 30 mm. rise in 7 unanesthetized dogs. This unit was approximately equal to the Goldblatt unit.

By the methods that were used in the preparation of the dialyzates, the pressor material was found to be slowly dialyzable through a cellophane membrane. It was not destroyed by freezing or lyophilizing. The pressor material which was present in minute quantities in the dialyzates could be extracted into butanol from the acidified concentrated salt solution which was essentially what the dialyzates were at this stage in their chemical processing. The pressor material was adsorbable onto alumina from the butanol or 90 per cent ethanol and could be eluted from it by the addition of water. These properties are characteristic of hypertensin.

Ten dialyzates from hypertensive dogs that contained hypertensin were tested for destruction of the pressor effect of this material by incubation with hypertensinase and trypsin. Several control tests were performed using heat-inactivated trypsin and hypertensinase. The pressor effects of the dialyzates were destroyed by incubation with trypsin and hypertensinase.

A large quantity of a material such as hypertensin must be available if a complete study of its chemical components and biologic characteristics are to be undertaken. No such comprehensive study could be done on the pressor material obtained in the dialyzates from the circulating blood of the dogs, because it was present in such small amounts. The number of chemical and biologic tests for identifying it had to be limited to the ones that gave the most information as to its nature. The results of the chemical and biologic tests given above show that the pressor material obtained had all of the general properties and characteristics of hypertensin. An analysis of a pooled sample of 22 different preparations gave the following average composition for each 300 ml. of chemically prepared dialyzate: sodium, 0.164 mEq.; potassium, 0.0079 mEq.; chloride, 0.177 mEq.; glucose, 1.0 mg.; urea nitrogen, 0.33 mg.; total nitrogen, 1.23 mg.; total solids, 24.5 mg.

One control preparation was run for each experiment in order to determine the amount of hypertensin that was lost during the processing of the dialyzate. The control preparation consisted of 300 ml. of dialyzate, which contained no pressor material, obtained from normal dogs to which 0.02 to 1.0 unit of hypertensin was added, and worked up in the same manner as the dialyzate from the experimental animals. Forty-nine such control preparations were done and the recovery of hypertensin ranged from 50 to 80 per cent with an average yield of 60 per cent.

Experiment 1. Eleven dogs, made hypertensive by means of moderate constriction of one or both renal arteries by a Goldblatt clamp,[6] were subjected to dialysis of their blood in the artificial kidney. Nine normal dogs were also subjected to dialysis in the same manner to determine whether there was a significant difference in the amount of hypertensin recovered from the dialyzates of the hypertensive dogs compared with that recovered from the normal animals. (See tables 1 and 2.)

Experiment 2. Six bilaterally nephrectomized dogs were subjected to dialysis to determine whether hypertensin was present in the circulating blood of animals with both kidneys removed. A pressor material was found in the dialyzate of only 1 of the dogs and it was not present in sufficient amounts to determine whether or not it was hypertensin.

TABLE 1.—*Dogs with Benign Experimental Renal Hypertension*

Number	Pressure	Operations	Number of days dog has had hypertension	Units of hypertensin per liter of dialyzate	
				1st 90 min. period of dialysis	2nd 90 min. period of dialysis
42	140	LK	4	1st flask 0.20 U/L 2nd flask 0.33 U/L	1st flask 0.08 U/L 2nd flask 0.09 U/L
43	150	LK	6	1st flask 0.21 U/L 2nd flask 0.20 U/L	1st flask 0.08 U/L 2nd flask 0.11 U/L
32	200	LK & RK	7	1st flask 0.33 U/L 2nd flask 0.33 U/L	1st flask 0.03 U/L 2nd flask 0.02 U/L
28	165	LK & RK	10	1st flask 0.20 U/L 2nd flask 0.32 U/L	1st flask 0.20 U/L 2nd flask 0.08 U/L
29	175	LK	15	1st flask 0.08 U/L 2nd flask 0.10 U/L	1st flask—0 2nd flask—0
16	165	RK & LK	21	1st flask 0.08 U/L 2nd flask 0.11 U/L	1st flask 0.04 U/L 2nd flask—trace
16	155	RK & LK	25	1st flask 0.08 U/L 2nd flask 0.02 U/L	1st flask 0.07 U/L 2nd flask 0.04 U/L
31	205	LK & RK	29	1st flask 0.42 U/L 2nd flask 0.33 U/L	1st flask—trace 2nd flask—trace
30	150	LK & RK	36	1st flask 0.08 U/L lost	1st flask—trace 2nd flask 0.08 U/L
27	155	LK & RK	40	1st flask 0.05 U/L 2nd flask 0.02 U/L	1st flask—trace 2nd flask—trace
27	155	LK & RK	90	1st flask 0.07 U/L lost	1st flask 0.08 U/L 2nd flask 0.05 U/L

TABLE 2.—*Normal Dogs*

Dog Number	Units of hypertensin per liter of dialyzate	
	1st 90 min. per. of dialysis	2nd 90 min. per. of dialysis
34	1st flask—trace 2nd flask—0.04 U/L	1st flask—0 2nd flask—0
37	1st flask—trace 2nd flask—0.03 U/L	1st flask—0 2nd flask—0
38	1st flask—0.08 U/L 2nd flask—0	1st flask—0.04 U/L 2nd flask—0
38	1st flask—0.04 U/L 2nd flask—0.04 U/L	1st flask—trace 2nd flask—0
39	1st flask—0.04 U/L 2nd flask—0.04 U/L	1st flask—0.04 U/L 2nd flask—0.04 U/L
43	1st flask—0.06 U/L 2nd flask—0.03 U/L	1st flask—0.03 U/L 2nd flask—trace
44	1st flask—0.05 U/L 2nd flask—0.06 U/L	1st flask—0.04 U/L 2nd flask—trace
45	1st flask—trace 2nd flask—trace	1st flask—trace 2nd flask—broken
42	1st flask—trace 2nd flask—0	1st flask—0 2nd flask—0
32	1st flask—trace 2nd flask—trace	1st flask—trace 2nd flask—trace

TABLE 3.—*Recovery Experiments. Injection of Hypertensin into Bilaterally Nephrectomized Dogs*

Dog Number	Elevation of blood pressure	Amount of hypertensin injected	1st 90 min. per. of dialysis	2nd 90 min. per. of dialysis
	mm. Hg	*unit/mm.*	*u/L*	*u/L*
49	25 25	0.43	1st—0.2 2nd—0.17	1st—0.08 2nd—0.07
51	30 30	0.43	1st—0.11 2nd—0.07	1st—0.08 2nd—0.09
51	25 30	0.43	1st—0.07 2nd—0.08	1st—0.08 2nd—0.08
53	20 20	0.43	1st—0.08 2nd—0.04	1st—0.08 2nd—0.08
54	35 30	0.43	1st—0.05 2nd—0.05	1st—0.05 2nd—0.06
55	35 30	1	1st—0.33 2nd—0.22	1st—0.17 2nd—0.22
56	25 35	1	1st—0.22 2nd—0.22	1st—0.22 2nd—0.22

Experiment 3. Six bilaterally nephrectomized dogs were dialyzed for two consecutive 90-minute periods, during which they were infused with hypertensin. The hypertensin was administered intravenously at a constant rate by means of a syringe which was driven at a constant speed. Four dogs received 0.43 unit of hypertensin per minute and 2 dogs received 1 unit of hypertensin per minute. The first group of animals received 36 units of hypertensin during each 90 minute period and the second group 90 units. The infusion of hypertensin elevated the blood pressure 20 to 30 mm. Hg. in the first group of animals, and 25 to 35 mm. Hg in the second.

This group of experiments was performed for two reasons. (1) In order to determine if the recovery of hypertensin from the dialyzates would be in the same order of magnitude as was the hypertensin which was recovered from the dialyzates of the dogs with experimental renal hypertension. (2) To determine whether the same amount of hypertensin was recovered in the second 90 minute period of dialysis as in the first (see table 3).

Discussion

Hypertensin has been dialyzed out of the blood of normal dogs and dogs with benign experimental renal hypertension by means of an artificial kidney. It was recoverable in significantly larger amounts from the animals in the early phases of experimental hypertension than in those with long continued elevation of their blood pressures or in the normal dogs. (Dog 31 had renal insufficiency and died of malignant hypertension.)

The recovery of hypertensin from bilaterally nephrectomized dogs infused with this substance shows that the methods used for its recovery in these experiments would have demonstrated it, if it were present in sufficient amounts in the circulating blood of the intact dog. Tables 1 and 2 show that there was a marked drop in the amount of hypertensin recovered during the second 90 minute period of dialysis in the hypertensive and in the normal animals. There was no decrease, however, in the amount of hypertensin recovered in the second 90 minute period in the animals that received a constant intravenous infusion of this material. This finding ruled out the possibility that the cellophane membrane became progressively less permeable to the hypertensin molecule, and it means that there was less hypertensin circulating in the dogs' blood during the latter part of the experiments. It is true that the blood pressures of animals with experimental hypertension and hypertensive human beings tend to fall somewhat when they are put at complete rest. It may be inferred from this fact that less hypertensin is formed at such times and this could be an explanation for the decrease in the amount of hypertensin recovered from the dogs during the second 90 minutes of dialysis.

From the experimental data it is impossible to conclude with certainty that hypertensin is the vasoconstrictor material responsible for the elevation of blood pressure in benign experimental renal hypertension. The findings, however, do suggest this possibility, since at least in the majority of hypertensive dogs more hypertensin was recovered in the dialyzates from both the first and second periods than was found in the normal animals. It is also of interest, although it may be only a coincidence, that the amount of hypertensin recovered from the animals with early experimental renal hypertension and those which received a constant infusion of this material was of about the same magnitude.

The possibility that the experimental procedures were in themselves sufficient to cause the kidneys to form renin and thus liberate hypertensin into the blood could not be ruled out, for the application of the artificial kidney to the dogs created a large arteriovenous shunt. There was not, however, a fall in blood pressure when the dialyses were first started, so that a drop in the blood pressure could not be incriminated as the stimulant for the production of renin and the liberation of hypertensin. The abnormal position of the dogs during the dialyses, the injection of morphine and atropine, and the transfusion of 400 ml. of blood from a uremic donor dog could possibly have stimulated the production of renin in the kidneys of the dogs that were dialyzed. If these assumptions were true, they still do not explain why more hypertensin was obtained from the hypertensive than from normal dogs, when they were subjected to the same experimental procedures.

If renin were present in the circulating blood, its action on its substrate, hypertensinogen, could be sustained or even accelerated during its passage through the artificial kidney because of its extravascular position. For this reason, it cannot be concluded with finality that the methods employed are a test for hypertensin alone, but may be a test for renin as well. It would be unwise, therefore, to make a strict comparison of the amount of hypertensin recovered in the infusion experiments with the amounts recovered from the hypertensive or normal dogs.

A simpler method for isolating hypertensin from the blood than by dialysis in an artificial

kidney must be developed before there can be a definite conclusion reached as to whether hypertensin is the chemical mediator responsible for the elevation of the blood pressure in experimental renal hypertension. The results obtained in these experiments suggest that hypertensin may play an important role in initiating and maintaining the elevation of blood pressure at least in the initial phases of experimental renal hypertension. Indeed hypertensin was recovered from the dialyzates of all of the hypertensive dogs even those with chronic benign experimental renal hypertension, although the amount is much reduced and tends to overlap that recovered from an occasional normal dog. These findings are in agreement with those of Goldblatt.[7]

Summary

1. Hypertensin has been dialyzed out of the circulating blood of normal dogs as well as dogs with experimental renal hypertension.

2. Hypertensin was obtained in significantly larger amounts from the animals in the early phases of experimental renal hypertension than in those with long continued elevation of their blood pressure or in normal dogs.

3. A new method for the recovery of hypertensin from the dialyzate, which yielded a 50–80 per cent recovery of this material, has been described.

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An Intracardiac Manometer: Its Evaluation and Application

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The miniature intracardiac manometer supplied a method for recording artefact-free pressure tracings from the heart and great vessels of man and the intact animal. This instrument has been applied to the procedure of cardiac catheterization. It has also been used to demonstrate that if motion artefacts can be minimized, the central pulse can be recorded with reasonable accuracy by means of manometric systems with relatively poor dynamic response. Illustrations of pulse waves within the heart and great vessels of man and dogs and the effects of varying the dynamic response of the recording system are included.

THE WIDESPREAD acceptance and application of cardiac catheterization in diagnosis of congenital heart disease has required the accurate recording of changes in intracardiac pressure. In spite of the physical difficulties of recording through a long, narrow-bore cardiac catheter, it has been found that manometer-catheter systems with reasonably adequate dynamic response can be evolved.[1-3] Even when such manometer-catheter systems are used, the recordings of pressure obtained from the right ventricle and pulmonary artery of human beings are often obviously distorted by artefacts.[1, 2]

The artefacts are, for the most part, produced by pressures generated in the lumen of the catheter by the acceleration and deceleration of the contained column of fluid, associated with movements of the catheter imparted by the heart beat.[1, 2]

This type of motion artefact can be minimized if the movable mass coupled to the manometer is very small so that the reactive forces and consequent pressures generated by movement are correspondingly reduced.

A manometer made sufficiently small to be attached to the intracardiac end of a cardiac catheter would have this characteristic. It would also avoid other serious difficulties associated with recording through a long narrow plastic tube, such as damping factors, entrapped air bubbles and variation of physical characteristics of the catheter which accompany change of temperature.

Gauer and Gienapp[4, 5] designed such an instrument according to the principles first outlined by Wetterer.[6] The manometer as applied in cardiac catheterization is illustrated in figure 1. The brass housing of the miniature manometer accommodates two transformers, the secondary coils of which are wound in opposite directions. The relative coupling of the coils varies with the movements of a soft iron core mounted on the base of a tiny piston which is pressurized by the intracardiac or vascular pressure. The manometer is attached to an 8 F. cardiac catheter and projects 1.2 cm. beyond its woven tip. Amplification of approximately 150,000 to 1 is required and carrier-wave amplifiers have been used.

METHODS

A dynamic pump or pistonphone, described by Lambert and Jones, was employed to analyze the responses of this new manometer.[1, 2] This device generates equal amplitude pressure variations of variable frequency, by means of a piston moving in a small glass cylinder over a column of air and fluid. The piston is driven by means of an eccentric coupled to a variable speed electric motor. The manometer to be evaluated is fitted to the chamber which contains fluid by means of suitable airtight adapters.

An electromagnetically driven pressure oscillator,[7] simpler in construction and easier to use than the instrument just described was employed for a portion of these studies. This instrument consists of a cylindric lucite chamber filled with liquid, one

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end of which consists of a stiff, brass diaphragm coupled to a magnetic pen motor which imparts a sinusoidal movement to the membrane. A strain-gage manometer is coupled directly to the opposite end and serves to monitor the variations in pressure produced in the chamber. The pen motor is driven by an electrical sine-wave oscillator. This type of dynamic testing device has three times the frequency range, approximately 1,000 cycles per second, of the piston type, but either device is satisfactory for evaluation and testing of manometers used for most physiologic recordings.

FIG. 1. Gauer-Gienapp intracardiac manometer attached to an 8 F. Cournand catheter.

In addition to the previously described dynamic oscillators, square-wave or step responses were also employed to establish the physical characteristics of the manometric systems. A modification of the exploding balloon technic, originally described by Frank, was employed.[8]

In order to evaluate the applicability of the intracardiac manometer to catheterization of human beings four large adult dogs under light pentobarbital sodium anesthesia were employed.* The manometer was passed through the external jugular vein into the chambers of the right side of the heart and into the pulmonary artery, and, by way of the carotid artery, into the aorta and left ventricle. After pressures were recorded from the intact animal the thorax was opened and respiration maintained by means of a pump. Pressures within the chambers of the heart were then recorded with a high-fidelity strain-gage system by direct puncture, and simultaneously with the intracardiac manometer.

Additional animals were subjected to extensive catheterizations of the right side of the heart and killed in three days to determine the extent of endocardial damage produced by catheters tipped with the Gauer-Gienapp manometer as compared to that produced by standard Cournand catheters.

RESULTS

The miniature intracardiac manometer has a natural frequency in excess of 1,000 cycles per second. It is relatively undamped, but, when coupled with an appropriate galvanometer (Heiland type G†), will give a response of equal amplitude from 0 to 50 cycles per second without peaks thereafter (table 1; see also top panel, fig. 7).

The manometer is relatively insensitive to temperature. A zero or base-line shift corresponding to 6 to 7 mm. of mercury occurred with the change from room temperature (23 C.), to body temperature (37 C.). Such a zero shift did not affect the magnitude of the static or dynamic calibrations and was avoided in practice by calibrating the instrument in a water bath at body temperature before and after insertion into the body.

Sensitivity of the manometer depends on the gain available in the amplifier. In these studies

TABLE 1.—*Dynamic Response of Strain-Gage and Gauer-Gienapp Manometers in Per Cent of Static Sensitivity*

	Cycles Per Second								
	10	20	30	40	60	80	100	150	170
Strain gage with 15 gage needle, per cent	98	103	102	100	97	97	98	106	124
Gauer-Gienapp manometer, per cent	102	105	103	97	84	74	62		

* Animal experiments conducted with the assistance of Dr. H. E. Essex, Institute of Experimental Medicine, Rochester, Minnesota.

† Manufactured by the Heiland Research Corporation, Denver, Colorado. Natural frequency 150 cycles per second, sensitivity 0.43 microampere per millimeter at 1 meter; damping used was approximately 200 per cent of critical.

a range of deflection from 0.3 to 2 mm. per millimeter of mercury was employed.

Hysteresis is negligible with the Gauer-Gienapp manometer, being less than 0.01 per cent.

The artefact which results from motion is almost absent with this manometer as illustrated in figure 2. A conventional 8 F. cardiac catheter, attached in an optimally damped strain-gage system (response within ±5 per cent of 28 cycles per second with no peaks thereafter), and a Gauer-Gienapp manometer were bound together so that they were subject to identical motion and the pressures generated by various motions were recorded at the same sensitivity. The absence of artefact with the Gauer-Gienapp manometer during circular, to-and-fro, pendular, side-to-side and rotating motion was evident. Numerous pressure recordings from the heart and great vessels of man and dogs were uniformly free of recognizable artefact of this type when the intracardiac manometer was used (figs. 3 to 6, 8 and 10).

Figure 3 demonstrates characteristic contours of the central pulse waves recorded with the Gauer-Gienapp manometer in intact dogs. The systolic summits in the left ventricle are noted to be of a slowly ascending or plateau type, while those of the right ventricle are peaked with a rapidly descending slope.

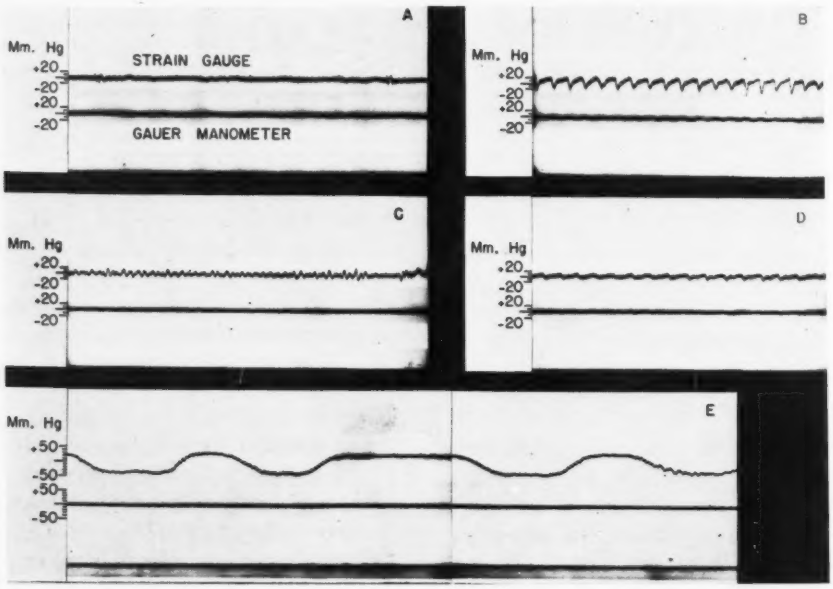

FIG. 2. Artefacts. Pressures generated by simultaneous identical motions of the intracardiac ends of two 8 F. cardiac catheters, one with a Gauer-Gienapp manometer attached to the intracardiac tip and the other filled with fluid and with the external end attached to strain-gage manometer, this overall system being optimally damped. *A*, vertical circular motion of the tips of both catheters through a diameter of 10 cm. at rate of 1 cycle per second; *B*, pendular motion along the axis of the catheter approximately 4 cm. in amplitude at rate of 2 cycles per second; *C*, pendular motion transverse to the axis of the catheter through a distance of 4 cm. at rate of 2 cycles per second; *D*, catheter tip fixed and oscillatory motion imparted to the shaft of the catheter; *E*, catheter tip rotated through an arc of 180° on a radius of 50 cm.

The catheter has been passed from the carotid artery down the aorta into the iliac artery in intact dogs and continuous pressure tracings have been taken as the manometer was slowly drawn back into the carotid artery. Figure 4 shows such a recording and illustrates the marked variations in the contour of the pulse waves recorded with the micromanometer at

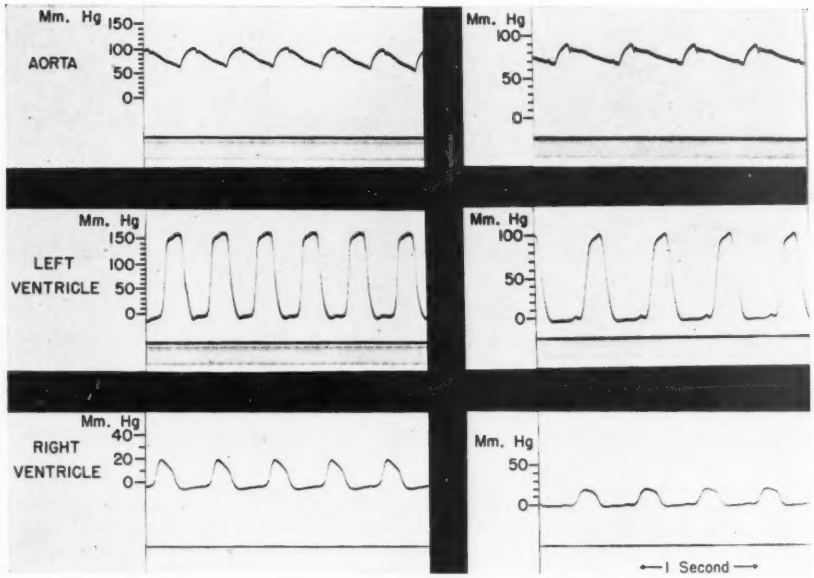

FIG. 3. Pressure pulse contours recorded with the Gauer-Gienapp intracardiac manometer in the aorta, left and right ventricles in 2 intact dogs.

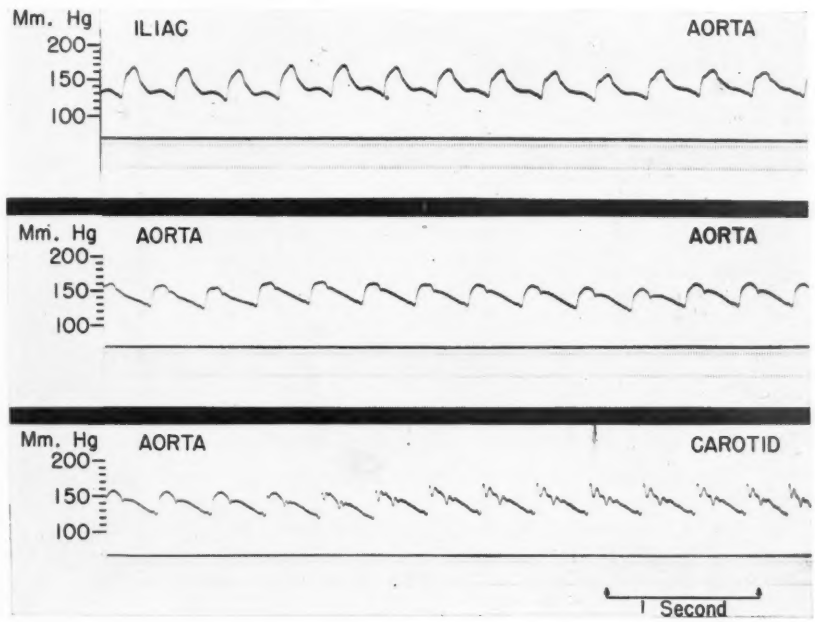

FIG. 4. Continuous recording of pulse waves in the intact dog while slowly withdrawing the Gauer-Gienapp manometer from the iliac artery through abdominal and thoracic aorta to the carotid artery.

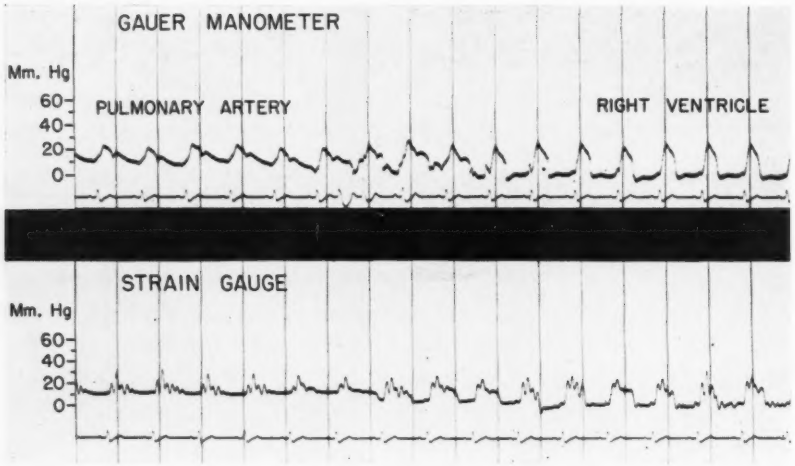

FIG. 5. Tracing from human being during the withdrawal of the catheter from the pulmonary artery through the pulmonic valve into the right ventricle. The top tracing was obtained with the Gauer-Gienapp manometer and the bottom tracing from the same patient by means of an optimally damped system with the strain gage attached to the external end of a conventional Cournand catheter, size 8. The apparent artefact in the midportion of the upper tracing is due to the position of the manometer within the pulmonic valve. The distortion of the lower tracing is due to the artefact produced by the motions of the catheter imparted by the heart beat.

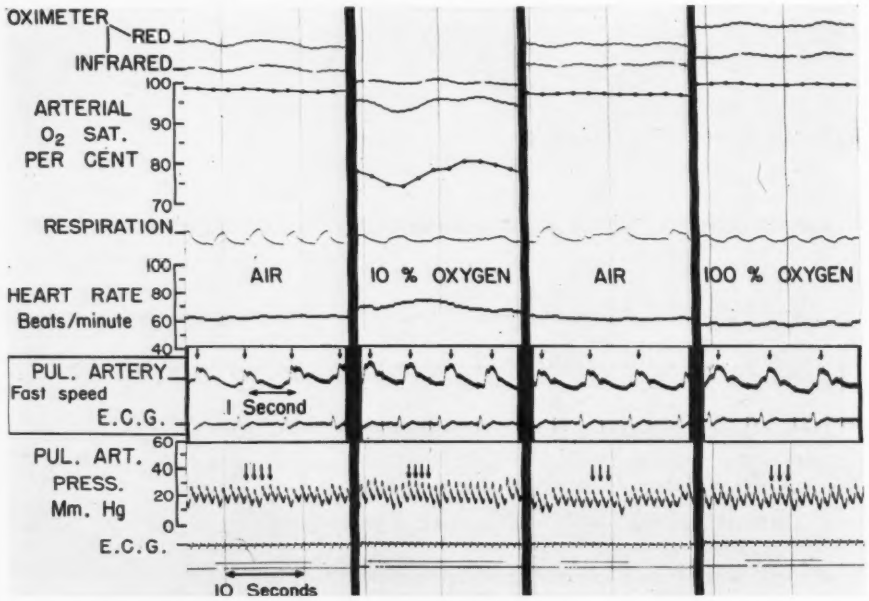

FIG. 6. Tracings from pulmonary artery of human being during inhalation of air, 10 per cent oxygen, air and 100 per cent oxygen. The inserts showing the contours of pulse waves are from simultaneous records photographed at a faster speed. The arrows indicate the identical pulses on the fast and slow speed recordings.

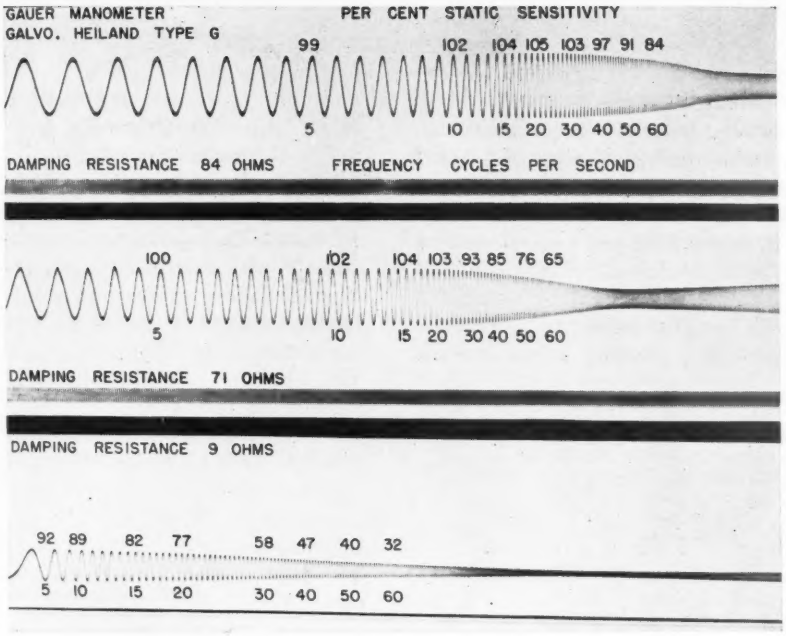
GAUER MANOMETER
GALVO. HEILAND TYPE G
PER CENT STATIC SENSITIVITY
99
102 104 105 103 97 91 84
5
10 15 20 30 40 50 60
DAMPING RESISTANCE 84 OHMS
FREQUENCY CYCLES PER SECOND
100
102 104 103 93 85 76 65
5
10 15 20 30 40 50 60
DAMPING RESISTANCE 71 OHMS
DAMPING RESISTANCE 9 OHMS
92 89 82 77 58 47 40 32
5 10 15 20 30 40 50 60

FIG. 7. Response of the Gauer-Gienapp intracardiac manometer to equal amplitude pressure variations imparted by the pistonphone pressure oscillator. The three damping conditions illustrated were employed to record the pressure tracings shown in figure 8.

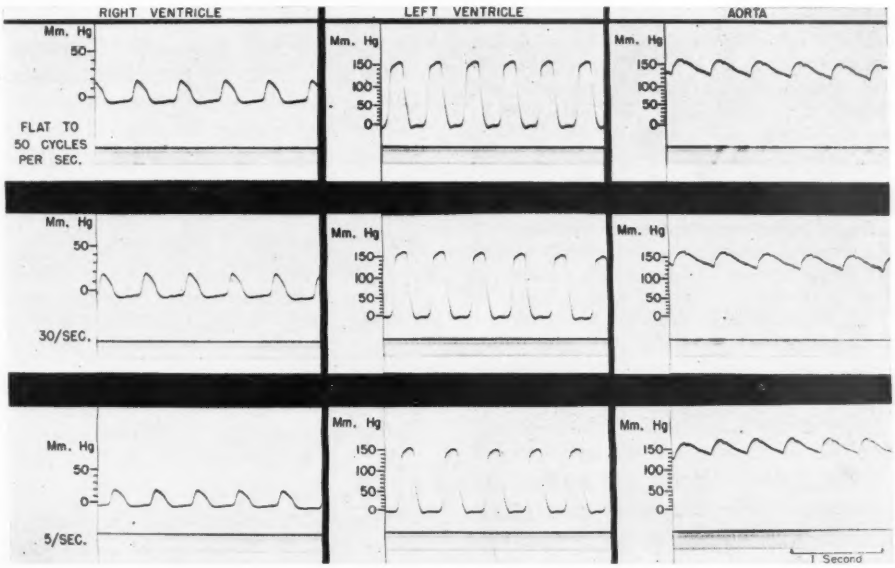

FIG. 8. The effect of rapid interchange of manometric systems with different characteristics of dynamic response (fig. 7) on the contours of pulse waves recorded from the right ventricle, left ventricle and arch of the aorta in an intact dog. Top panels recorded with a system with a dynamic response flat to 50 cycles per second, middle panels recorded with system flat to 30 cycles per second and bottom panels recorded with system flat to 5 cycles per second. Although the sensitivity of the three systems varies slightly there is little apparent or measurable change in the pulse contours obtained from the ventricles or the aorta.

different positions in the arterial tree. These results are similar to those obtained by Hamilton and Dow[9] by individual pressure tracings recorded after direct punctures at different sites in the arterial tree.

Figure 5 shows pressure tracings from a human being recorded during slow withdrawal of a conventional cardiac catheter and of a catheter with the Gauer-Gienapp manometer attached from the pulmonary artery into the right ventricle. The artefacts induced by the motion of the fluid column in the conventional catheter are evident. This serves to emphasize the importance of the distortion produced by motion of the catheter.

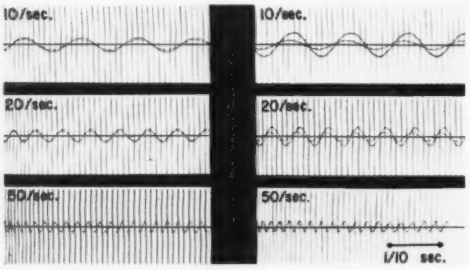

FIG. 9. The time lag in recordings with manometric systems with different characteristics of dynamic response.

Three panels on the left were obtained with a manometric system with a dynamic response which was flat to 50 cycles per second (top panel, fig. 7). The sine wave with the slightly greater amplitude was recorded from the Gauer-Gienapp manometer and the other from the strain gage directly coupled to the pressure chamber and monitoring the pressure changes produced in the electromagnetic pressure oscillator. It will be noted that there is no demonstrable shift in phase or delay in time through the range of equal amplitude response of the manometer.

Three panels on the right were obtained utilizing the over-damped system (flat to 5 cycles per second) illustrated in the bottom panel of figure 7. The time delay was 0.01 second at 10 cycles per second and decreased to approximately 2 milliseconds at 50 cycles per second.

The inhalation of various gas mixtures was associated with definite changes in the contour of the pulse wave in the pulmonary artery of human subjects as well as changes in the systolic and mean pressures (fig. 6). The effect of inhalation of low oxygen mixtures on systolic and mean pressures has been reported by others.[10–13] The Gauer-Gienapp manometer makes it possible in addition to demonstrate effects on the contour of the pulse wave in the pulmonary artery.

The ability to obtain accurate artefact-free tracings with the Gauer-Gienapp manometer, supplied a direct approach to the problem of the dynamic characteristics necessary in a manometer to reproduce the central pulse accurately. This could be accomplished readily since variation in the resistance of the shunt across the galvanometer, that is, electrical damping, produced immediate, easily reproducible changes in the dynamic response of the over-all manometric system. The dynamic responses of the three systems used are illustrated in figure 7. The three systems were immediately interchangeable by flicking a switch. The dynamic response of the first system as determined by the pressure oscillator was uniform to 50 cycles per second but was reduced to 84 per cent at 60 cycles per second; the next was uniform to 30 cycles per second and down to 65 per cent at 60 cycles per second, and the last was uniform to but 5 cycles per second and was reduced to 32 per cent at 60 cycles per second. Rapid interchange of these recording systems in the dog with closed thorax produced little apparent change in the contour of the pulse wave (fig. 8). Although the sensitivity of three systems varies slightly there is no measurable change in the systolic, diastolic or mean pressure.

It is realized that the shift in phase or delay in time is increased in a highly overdamped system (lower panel, fig. 7) but still it is of small magnitude. The electromagnetic oscillator with monitoring strain gage made it possible to record the actual sine-wave pressure which occurred within the oscillator simultaneously with that being recorded through the manometric system (fig. 9). It can be seen that in the optimally damped system there was a constant delay through the range of equal amplitude response, the magnitude of which was negligible for practical purposes (left 3 panels, fig. 9). In the overdamped system the delay in time was greatest at low frequencies and decreased with higher frequencies (right 3 panels, fig. 9). The magnitude of the delay was, however, relatively

small: approximately 0.01 second at 10 cycles per second and about 2 milliseconds at 50 cycles per second. Because of the apparent low fundamental frequencies in the normal central pulse and because the actual delay in time was so small, little distortion was evident between the tracings obtained with these two systems of widely different dynamic responses.

This type of comparison also was employed in dogs with open thorax. The pressure tracings from an intracardiac micromanometer were monitored by simultaneous pressure recordings from the same cardiac chamber obtained by means of a special strain gage attached to a 15 gage needle introduced into the chamber by direct cardiac puncture. The strain-gage system had an equal amplitude response to 100 cycles per second and a peak response of 124 per cent at 170 cycles per second (table 1). Figure 10 does not demonstrate any appreciable differences in the appearance of pressures from the pulse waves recorded with the two different systems.

In the dogs on which necropsy was performed to determine the degree, if any, of endocardial damage produced by cardiac catheterization, it was found that the catheters tipped with the micromanometer produced no more and in some instances even less damage than the conventional 8 F. catheter.[14, 15]

Comment

It has been shown that reasonably satisfactory manometric systems can be obtained for recording from the external end of a conventional cardiac catheter, but that the artefact due to motion of the catheter produced by the heart beat is of such magnitude as to compromise seriously pressure recordings obtained therefrom. In application of the miniature intracardiac manometer, emphasis has been placed on the elimination of this motion artefact since it is one of the major considerations in obtaining satisfactory pressure tracings from the human being during cardiac catheterization.

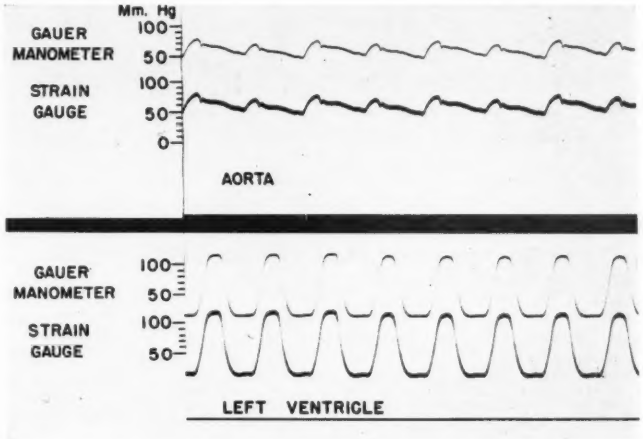

FIG. 10. Simultaneous recordings from the Gauer-Gienapp intracardiac manometer and a special strain-gage system recording by direct intracardiac puncture in a dog with thorax opened. The strain-gage manometer system had essentially an equal amplitude response to sine-wave pressure variations of from 0 to more than 100 cycles per second (table 1).

With the provision that optimally or overdamped manometric systems capable of reproducing sine-wave pressure variations of more than 5 cycles per second are used, the degree of fidelity of response to higher-frequency pressure variations is of less importance in obtaining accurate pressure recordings from a catheter than is the artefact due to motion of the catheter. Such artefacts may amount to 20 mm. of mercury (fig. 2), as compared to the little measurable or detectable difference in the tracings of central pulse waves recorded with widely divergent dynamic systems (fig. 8). Apparently in the dog, in which the normal heart rate is more rapid than that of man, the static and dynamic components of the central pulse can be reproduced

faithfully with a considerably poorer dynamic system than is usually deemed necessary.[16]

The analysis of the manometers used was carried out with dynamic pressure oscillators of two types, the pistonphone and the electromagnetic oscillator. These instruments are useful in determining the actual responses of manometers to rapidly oscillating pressure changes, such as are present in the vascular system. Evaluation of recording manometric systems in this manner would supply a much needed base line for comparison of the pressure tracings obtained from various laboratories which use different manometric systems, the dynamic responses of which are often poorly defined.

Summary and Conclusions

The application of a new miniature intracardiac manometer has been demonstrated in the catheterization of animals and human beings. Artefact-free, high-fidelity tracings of pulse waves were obtained.

The results indicate that the contour and magnitude of the central pulse can usually be recorded with reasonable accuracy with a manometric system which possesses a uniform sensitivity out to 5 cycles per second but only 32 per cent response at 60 cycles per second.

The dynamic response is of less importance than the artefacts associated with motion of the catheter in producing the poor intracardiac pressure tracings usually obtained with conventional cardiac catheter-manometer systems.

Recordings obtained from the pulmonary artery of human beings indicate that inhalation of gas mixtures of different oxygen content may be associated with changes in the contour of the pulse wave of the pulmonary artery as well as changes in the systolic, diastolic and mean pressures in the pulmonary artery.

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The Lack of Effect of Oral Doses of Cinchona Alkaloids on the Circulation of Dogs with Renal Hypertension

A Contrast to Their Action in Neurogenic Hypertension

By INEZ GREENE, M.S., AND EDWIN P. HIATT, PH.D.

The effect of repeated oral doses of quinine and quinidine on the circulation of dogs with renal hypertension was studied with measurements of arterial blood pressure and renal hemodynamics. Alkaloid concentrations up to the toxic range had little effect on the blood pressure or renal blood flow. It is pointed out that this lack of effect is in contrast to the vasodilator action of these agents in normal and neurogenic hypertensive dogs. These experiments are interpreted as constituting support for the thesis that the cinchona alkaloids have their vasodepressor effect by virtue of a blockade of sympathetic neuromuscular vasomotor junctions.

IT HAS been shown in this laboratory that orally administered cinchona alkaloids cause renal vasodilatation in normal dogs without much change in arterial blood pressure.[1] In dogs with experimental neurogenic hypertension these alkaloids cause a fall in the blood pressure as well as renal vasodilatation when administered in repeated oral doses.[2] For a long time it has been known that when these drugs are given intravenously there is a sharp fall in blood pressure. Nelson, in a series of papers published in 1927, investigated this phenomenon and concluded that the depressor effect of intravenous quinine and quinidine was due to peripheral vasodilatation brought about partly by blockage of the vasomotor nerve endings and partly by a direct action on the arteriolar smooth muscle.[3] He demonstrated that these drugs would antagonize the circulatory effects of epinephrine or splanchnic nerve stimulation.[4] We have recently confirmed these observations, with measurements of the effective plasma concentrations of alkaloid.[5]

It occurred to us that it might be possible, in dogs with renal hypertension, to assay the importance of the depressor action of these drugs directly on the smooth muscle of the arterioles or on the myocardium as separate from their sympatholytic effects. In such animals the hypertension is regarded as due to a humoral agent acting directly on the smooth muscle of arterioles with some stimulating action on the myocardium but with little contribution from sympathetic vasoconstrictor nerves.[6] The experiments reported here show the lack of effect of repeated oral doses of quinine and quinidine on dogs with renal hypertension in contrast to the decrease in blood pressure seen with the same regimen in dogs with experimental neurogenic hypertension.

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PROCEDURE

The experimental animals used in this work were female dogs, of the mongrel type, ranging in weight from 9 to 13.6 Kg. After control observations on blood pressure, the dogs were made hypertensive according to the method of Goldblatt.[7] Briefly this method consists of constricting the main renal artery on each side by applying to it a metal clamp. The operation was done in two stages allowing time after the first clamp was applied for the animal to recover before clamping the artery on the other side.

After the final operation, if the dog showed a sustained rise in mean blood pressure, it was considered to be a renal hypertensive animal. The 5 dogs used showed increases of 18, 33, 36, 43, and 69 per cent and had mean blood pressures ranging from 150 to 220 mm. Hg. All experiments, with the exception

of those on one dog, were done within one to three months after the animals became hypertensive. The one exception had repeated surgery over the course of a year in a vain attempt to increase its hypertension.

Direct measurement of the arterial blood pressure was carried out in the following manner. The unanesthetized dog was strapped loosely on its back to a dog board. Using 1 per cent procaine as a local anesthetic, the femoral artery was punctured with a 19 gage hypodermic needle which was connected to a tube filled with 5 per cent sodium citrate solution leading to a mercury manometer. After observing the mean pressure as registered by the mercury manometer, the needle was connected to a Hamilton membrane manometer and the blood pressure recorded photographically.

In preparation for doing renal clearances, 10 ml. of a mixture of 5 per cent creatinine and 2 per cent paraaminohippurate were given intravenously as a "priming" dose. Twenty ml. of the same solution were given subcutaneously into the loose skin on the flanks of the dog. Creatinine clearances were used as a measure of the glomerular filtration rate[8] and paraaminohippurate (PAH) clearances were taken as a measure of the effective renal plasma flow.[9] The dog was catheterized, and 30 minutes after the priming dose, the bladder was washed out with water, the urine discarded, and urine collection begun. Four urine samples were collected at 10 minute periods. No attempt was made to induce water diuresis in the dogs, but the bladder was washed out with water at the end of each collection period. Blood samples were taken at intervals for analyses of the concentrations of PAH, creatinine, and cinchona alkaloids.

After the control clearances, doses of one of the cinchona alkaloids were started. The usual procedure was to give four capsules of 15 mg. per Kg. on the first day and four or five capsules at approximately four hour intervals for the next two days, except that a lapse of about 10 to 12 hours occurred at night. This dosage schedule assured a level as high as or higher than that maintained in similar experiments on neurogenic hypertensive dogs.[2]

During the period of drug administration, the dog's blood pressure was checked once or twice daily, and renal clearance measurements were made on two different occasions while the dog was under the influence of the drug. When the drug was discontinued, at least a two day interval was allowed for complete disappearance of alkaloid from the plasma and blood pressure and clearances were again measured. The time usually required for an experiment was six days.

The analyses of plasma and urine concentrations of PAH were done according to the methods described by Smith and collaborators,[9] and creatinine concentrations were determined by the alkaline picrate method of Folin and Wu.[10] Quinine and quinidine concentrations in the plasma were analyzed according to the method of Brodie and Udenfriend.[11]

Results

The results of our experiments on all 5 dogs were essentially the same and are indicated in the accompanying graphic summaries of typical experiments.

In figure 1 it can be seen that a plasma concentration as high as 8 to 10 mg. per liter was achieved by repeated oral doses of quinidine sulfate as shown in the lower portion of the graph. In spite of the high concentration of alkaloid the blood pressure of this hypertensive dog showed little change as indicated by the height of the bars in the central part of the graph. In the upper section of the graph we have plotted the clearances of PAH, represented by the entire bar, and the clearances of creatinine as indicated by the black portion of each bar. Each bar represents an average of four clearance periods. The effective renal plasma flow (PAH clearance) and the filtration rate (creatinine clearance) increased in this experiment during the interval of the experimental period but without relation to the plasma alkaloid concentration.

In figure 2 a very similar experiment is shown except that quinine sulfate was administered. In this experiment the plasma alkaloid concentration was not so high as that shown in figure 1 but still in the range which caused a marked fall in the blood pressure of dogs with neurogenic hypertension.[2] In this experiment there was an apparent renal hyperemia during the administration of the drug, like that in normal dogs,[1] but this was not typical.

In figure 3 the contrast is shown between the effect of the cinchona alkaloids on dogs having renal hypertension and the effect on those with neurogenic hypertension. Blood pressures as percentages of the control pressure are plotted against plasma alkaloid concentrations. The control pressure in each case was taken as the average of the pressure just before the drug was started and that following withdrawal of the drug and its elimination from the plasma. The data from the dogs with renal hypertension (the solid symbols) indicate very little effect of the cinchona alkaloids on the blood pressure even at levels as high as 10 mg. per liter. There seems to be a slight hypertensive effect at low

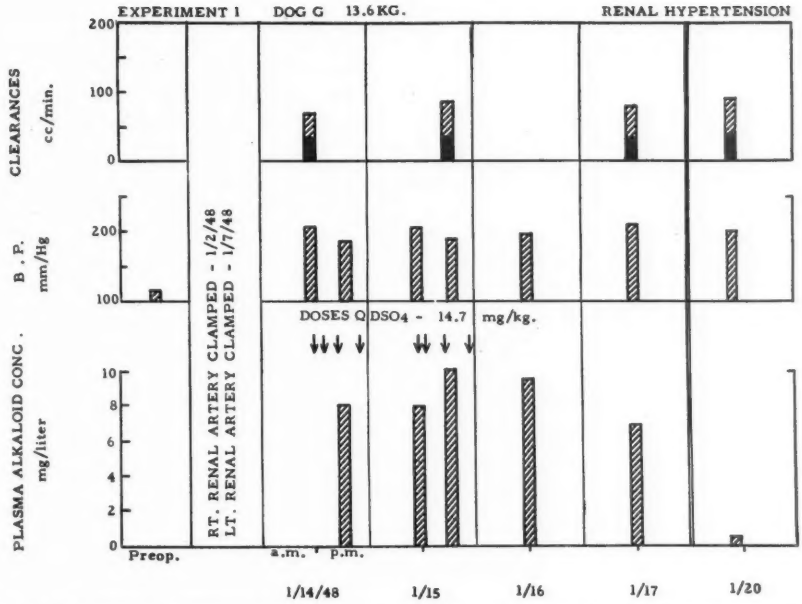

FIG. 1. The effect of repeated oral doses of quinidine sulfate on the blood pressure and renal clearances of a dog with renal hypertension. In the upper section of the graph, creatinine clearances are represented by the darkened part of the bars and PAH clearances by the entire bars.

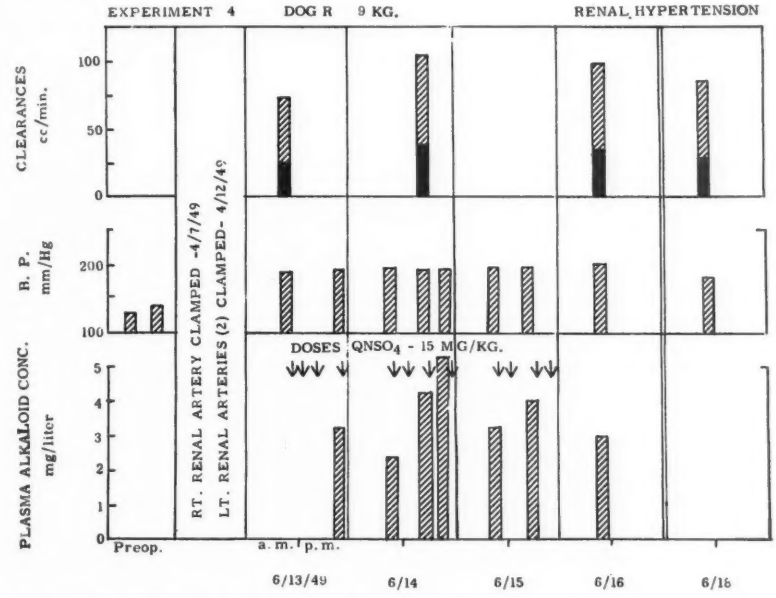

FIG. 2. The effect of repeated oral doses of quinine sulfate on the blood pressure and renal clearances of a dog with renal hypertension.

concentrations of quinine and a slight hypotensive effect at all concentrations of quinidine.

In contrast, the data on the neurogenic hypertensive dogs, taken from the work of Hiatt[2]

and shown as open symbols, show a marked downward trend of the blood pressure with increasing plasma concentrations of both alkaloids, apparent in spite of the wide scatter which is characteristic of blood pressure measurements in this type of preparation. It is obvious that the depressor effect of quinidine is greater than that of quinine.

In the beginning it was our intention to measure renal blood flow and glomerular filtration rate on all dogs before and after applying clamps to the renal arteries. But when it became apparent that in our hands the percentage of successful preparations was not high, we abandoned the control observations. However, we have compared the PAH and creatinine clearances of our hypertensive postoperative dogs with Houck's statistical analyses of these measurements in normal dogs.[12] Our mean values for both of the clearances, on the basis of body weight, were approximately 63 per cent of his mean values. In both the normal and hypertensive series, there was a very large scatter. The dogs used in our experiments showed no consistent change in renal hemodynamics with administration of cinchona alkaloids (another contrast with the neurogenic hypertensive dogs), but there was a general tendency for both effective renal plasma flow and glomerular filtration rate to increase with time after clamping the arteries.

The pulse rate, as in normal and neurogenic hypertensive animals, increased slightly or remained the same while the drug was being administered.

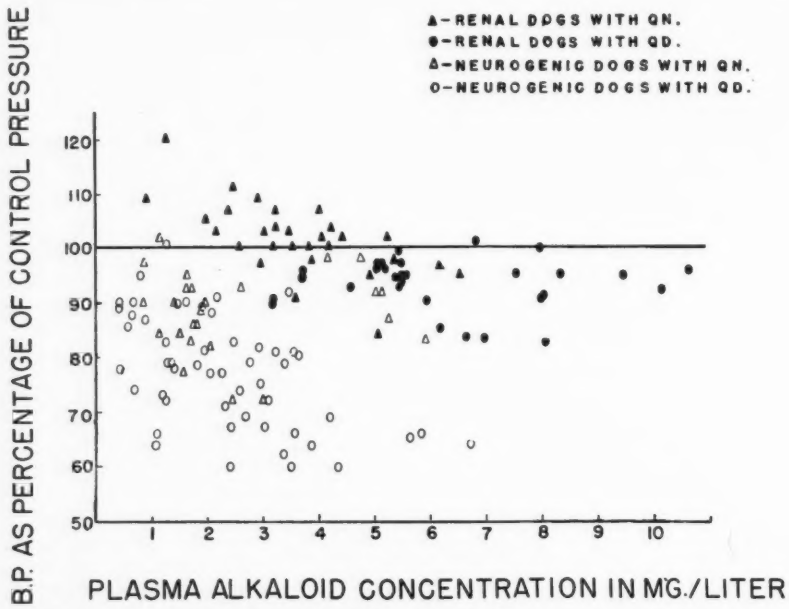

FIG. 3. The effect of oral quinine and quinidine on the blood pressure of renal hypertensive dogs in contrast with their effect on the blood pressure of dogs with neurogenic hypertension. One hundred per cent represents the average of two control blood pressure measurements, one preceding drug administration and the other, after the drug had been eliminated.

DISCUSSION

In considering how oral cinchona alkaloids cause a lowering of the blood pressure in dogs with neurogenic hypertension, one thinks of three possibilities: a sympatholytic action decreasing vasomotor tone, a relaxing action directly on arteriolar smooth muscle, or a depressor action on the heart. Of course there might be any combination of these three mechanisms. The first of these possible mechanisms

has been demonstrated by the antagonism of quinine and quinidine to the circulatory effects of epinephrine and splanchnic nerve stimulation.[8] The other two mechanisms apparently are not important as indicated by the above described lack of effect of the alkaloids (even at toxic plasma concentrations) on the blood pressure of dogs with renal hypertension. This view assumes that the maintenance of an arterial hypertension is evidence against an important depression of either arteriolar smooth muscle or myocardium.

Ferrer and her collaborators[13] reported that a single oral dose of quinidine sulfate (0.8 Gm.) in human subjects with and without cardiovascular diseases caused, in most instances, a fall in arterial pressure, but cardiac output, as determined by right heart catheterization, did not show any measurable change in those patients in whom there was a normal control output. Those patients with low cardiac outputs and elevated right ventricular systolic pressures responded with a shift toward normal values. The authors suggest that the fall in arterial blood pressure following quinidine is due largely to peripheral vasodilatation, but they also present electrocardiographic evidence for an effect on the myocardium.

It seems pertinent to mention that the plasma concentrations of cinchona alkaloids obtained in our experiments are not out of the range encountered in clinical use of these drugs. Sokolow and Edgar[14] have reported that 75 per cent of a series of 30 patients with auricular fibrillation converted to normal rhythm at plasma concentrations between 4 and 9 mg. per liter. In a similar study Kalmansohn and Sampson[15] found somewhat higher levels at the time of conversion. The minimum plasma quinine concentration in man necessary to suppress a malaria infection has been observed to be from 5 to 10 mg. per liter, according to the species and strain of the parasite, while quinidine is effective at somewhat lower plasma concentrations.[16]

Summary

Female dogs were made hypertensive according to the renal ischemia method of Goldblatt. Repeated oral doses of quinine and quinidine sulfate were administered and the effect on blood pressure and renal clearances noted. A comparison was made between the effect of the drugs on renal and neurogenic hypertensive dogs.

1. The blood pressure of renal hypertensive dogs was not significantly lowered at plasma alkaloid concentrations as high or higher than those which caused a sustained depressor effect on the blood pressure of neurogenic hypertensive dogs.

2. Mean renal clearances (creatinine and PAH) of the renal hypertensive dogs were reduced to 63 per cent of normal values. No consistent change due to the alkaloids was observed though the clearances tended to increase with time after the renal arteries were clamped.

3. The maintenance of blood pressure at plasma alkaloid concentrations as high as 10 mg. per liter indicated that neither arteriolar smooth muscle nor myocardium was markedly depressed and strengthens our impression that the depressor action of these drugs in normal animals is primarily at sympathetic neuromuscular vasomotor junctions.

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The Effect of Digitoxin on Sodium Excretion, Creatinine Clearance and Apparent Cardiac Output

By M. J. Greve, M.D., E. E. Eddleman, Jr., M.D., K. Willis, S. Eisenberg, M.D., and T. R. Harrison, M.D.

During the initial phase of decline in cardiac output following the administration of digitoxin to normal subjects, sodium excretion did not decline. Several days later, as cardiac output rose toward the normal level, sodium output decreased in most subjects. The possible implication of these results in relation to the regulation of sodium excretion is discussed.

IN RECENT years there has been an increasing interest in the possible relationship between alterations in hemodynamics and in sodium excretion. The suggestion has been made[1-3] that absolute or relative decline in cardiac output, consequent to peripheral circulatory failure or to heart failure, evokes an homeostatic mechanism which causes retention of sodium. The resulting increase in the volume of extracellular fluid and of blood would tend to increase venous return and to restore cardiac output, unless myocardial function were too gravely impaired.

The decline in sodium excretion during the states of circulatory failure has been thought by some observers to be mainly a consequence of diminished glomerular filtration[4-6] associated with decline in renal blood flow. Other investigators have failed to substantiate this concept. Thus normal glomerular filtration rates have been noted in a patient with congestive failure,[7] while failure of filtration rate to rise despite improvement of heart failure has also been reported.[8-10] The available evidence points toward increased reabsorption of sodium by the renal tubules as a more important factor than decline in filtration rate.

The unanswered question is whether the increase in tubular reabsorption of sodium is brought about by decline in cardiac output or by some other factor present in patients with circulatory failure. One possible approach to this problem would be to eliminate the complexities of circulatory failure, and study normal subjects in an attempt to elucidate the relationship between various hemodynamic factors and sodium excretion.

In previous reports[11-13] from this laboratory, it has been shown that sodium excretion is affected by hemodynamic factors other than cardiac output or glomerular filtration. Thus compression of the neck of sitting subjects caused increase in sodium excretion but had no detectable effect on cardiac output or creatinine clearance. Venesection of a degree too small to produce consistent changes in these functions, likewise, caused well marked decline in sodium excretion. On the other hand, changes in posture produced similar directional changes in cardiac output and in urinary sodium, with little or no change in filtration.

In order to complete the study of the relationship between these several functions in normal subjects, it would be desirable to reduce deliberately the cardiac output and observe the changes in sodium excretion.

In dogs and in normal men, digitalis has been shown to cause reduction in cardiac output[14-16] and in blood volume.[17-19] More recently the drug has been found to cause increase in thiocyanate space.[20, 21] It was thought, therefore, that an investigation of normal subjects receiving this drug might be of value in elucidating the relationship between sodium excretion and these hemodynamic factors.

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Procedure

Nine healthy male medical students were placed on a diet calculated to contain 1.0 Gm. of sodium daily, and to the food was added 2.0 Gm. of sodium chloride at breakfast and 2.5 Gm. sodium chloride at each of the other two meals. No attempt was made to control potassium intake. After the subjects had been on the diet for one week, or longer, control studies were made. Ventricular excursion and apparent cardiac output were estimated by the electrokymographic method, in the sitting position, before meals, at 7:00 a.m., 12:00 noon, and 5:00 p.m. Plasma creatinine clearances were measured, using a blood sample drawn before breakfast or lunch, and three eight-hour urine periods (7:00 a.m. to 3:00 p.m., 3:00 p.m. to 11:00 p.m., and 11:00 p.m. to 7:00 a.m.). On the following day, after an additional electrokymogram, 2.0 mg. of digitoxin were taken orally by each subject, in divided doses; 1.0 mg. at 8:00 a.m., 0.6 mg. at 12:00 noon, and 0.4 mg. at 5:00 p.m. No other digitoxin was given. Cardiac excursion and creatinine clearances were measured as on the control day. For the following three days, cardiac studies were made at 7:00 a.m., daily; and creatinine clearances were done from 7:00 a.m. to 3:00 p.m., daily. Sodium and potassium excretion in the urine were measured for three or four days prior to the administration of digitalis, and for four days thereafter. Serum potassium was determined on the day following digitalis administration. During these studies the subjects engaged in no strenuous exercise but carried on normal sedentary activities, including attending classes and studying. The experiments were conducted during the months of January, February, and March when sweating was at a minimum. It should be noted that digitalis was administered on one day only.

Electrocardiographic tracings were made just prior to the first and last doses of digitoxin. The second electrocardiogram showed minimal lowering of T waves. The subjects were weighed daily throughout the experiment, and blood pressure was measured each time an electrokymographic tracing for cardiac output was taken.

Methods

Cardiac outputs were calculated from the heart rates and the apparent stroke volumes as measured by the electrokymographic method, the original technic of Ring and associates[22] having been slightly modified.[23] The hemodynamic studies are being published in detail elsewhere,[24] and the data reported here are only the percentage variations from the average of control values. The quantitative accuracy of the electrokymographic method of measuring cardiac output has not yet been established, and there may be errors in the figures presented here for percentage change. On the other hand, the method appears to be reliable for detection of directional alterations and for obtaining a general guide as to their magnitude.

Endogenous creatinine clearances were measured by the method of Bonsnes and Taussky[25] as modified by Brod and Sirota.[26] Clearances are given over 24 hour periods based on plasma creatinines drawn once during that period. It has been reported since this work was done that, for greater accuracy of 24 hour clearance, plasma levels of creatinine should be determined at four to six hour intervals.[27] Hence the values for the first period of each day (7:00 a.m. to 3:00 p.m.) are probably more accurate than those for the subsequent periods. The latter are included in the data because they are probably significant where striking variations occurred. The creatinine clearance rather than the inulin clearance was measured, because it was believed preferable to have measurements over a period of several hours.

Urine sodiums were determined by the method of Hoffman and Osgood,[28] with the slight technical modifications which have previously been reported.

Urine and serum potassiums were measured colorimetrically by the method of Shohl and Bennett,[29] using the precipitation and washing procedures described by Consolazio and Dill.[30]

The observations on 3 additional subjects were discarded because their sodium excretions varied widely during the control period. In 2 instances in the reported subjects, single 24 hour sodium excretions were discarded in averaging the control days, but all of the data following digitalis administration are included.

Results

Alterations in apparent cardiac output, endogenous creatinine clearance, and urinary sodium are presented in table 1. The data are arranged according to the number of hours following the beginning of digitoxin ingestion. In all subjects the apparent cardiac output fell below the lowest control value at some time during the experiment. The degree and time of maximum decline varied. When the output was lowest most of the subjects had mild symptoms of lethargy, drowsiness, and anorexia. In all but 1 subject the apparent output had returned to within the control range at 72 hours.

The endogenous creatinine clearances were used as a measure of glomerular filtration rate. There was no parallel variation in cardiac output and creatinine clearance. From the average results shown in figure 1, it can be seen that filtration rate declined slightly throughout the experiment, though to a lesser degree than

did cardiac output. From the complete data in table 1 it is observed that in only 1 subject, J. M., did creatinine clearance fail to fall. In 2 subjects, C. C. and R. C., creatinine clearance rose to control levels as apparent cardiac output rose at the end of the experiment; and, in 1 individual, T. E., both functions were significantly below control values when the experiment was ended. In the 5 remaining subjects, however, filtration rate was still low after output had returned to control levels.

The sodium excretion for 24 hour periods and for the 7:00 a.m. to 3:00 p.m. period of each 24 hour interval are included in table 1. The eight hour results have been included because these time intervals correspond to the timing of the more accurate filtration rate measurements, and because the electrokymographic

TABLE 1.—*Effect of Digitoxin on Cardiac Output, Endogenous Creatinine Clearance and Urinary Sodium.*

Subject	Cardiac Output, % Change						Endogenous Creatinine Clearance, cc. per min.								
	Variation of Controls	Hours after Beginning of Digitoxin Administration					Control Day			Hours after Beginning of Digitoxin Administration					
		4	8	24	48	72	7 AM–3 PM	3 AM–11 PM	11 PM–7 AM	0–8	8–16	16–24	24–32	48–56	72–80
M. G.	− 8 to +12	−54	−54	−48	−39	− 8	129	(130)	(127)	139	(127)	(54)	108	117	—
J. B.	−13 to +11	−13	−22	−33	+ 4	—	161	(148)	(123)	141	(160)	(134)	157	130	—
J. M.	− 8 to +13	−38	−21	−18	+ 6	+ 6	99	(133)	(104)	88	(133)	(117)	115	—	99
C. C.	−13 to +31	−11	+13	0	−17	+ 8	130	(117)	(96)	110	(134)	(128)	115	—	124
T. E.	−13 to +13	+16	+24	−40	−29	−51	115	(131)	(99)	110	(106)	(94)	96	99	80
R. C.	−16 to +16	−41	−35	−41	−39	+ 2	110	(127)	(87)	104	(91)	(82)	77	97	121
H. W.	−20 to +15	−55	−35	−11	−25	+15	124	(103)	(92)	89	(81)	(75)	99	95	—
J. K.	−16 to +21	−24	−16	− 4	−46	−14	151	—	(131)	127	(144)	(147)	90	88	90
D. V.	− 5 to + 5	+12	+ 5	−23	−12	+21	176	(154)	(165)	159	—	—	179	144	92

Subject	Urine Sodium, *Gm.*								
	7 AM–3 PM Control Average Range	24 Hour Control Average and Range	Hours after Beginning of Digitoxin Administration						
			0–8	0–24	24–32	24–48	48–56	48–72	72–80	72–96
M. G.	1.41 (.9 to 1.7)	*3.33* (3.28 to 3.35)	1.25	*3.30*	1.44	*3.21*	1.07	*3.44*	—	—
J. B.	1.31 (1.1 to 1.5)	3.24 (2.94 to 3.64)	0.94	3.68	1.50	3.40	1.05	2.80	—	—
J. M.	1.24 (.5 to 1.9)	3.96 (2.59 to 5.52)	1.13	*2.79*	.89	*3.56*	1.22	*2.77*	.80	*2.44*
C. C.	1.11 (.6 to 2.0)	3.31 (2.25 to 4.45)	.47	3.15	1.78	5.12	1.06	2.42	1.63	3.58
T. E.	1.45 (.7 to 2.1)	*3.71* (3.24 to 4.18)	1.41	*4.13*	1.53	*4.01*	1.00	*2.73*	1.06	*2.58*
R. C.	1.12 (.8 to 1.3)	3.45 (3.15 to 3.86)	1.40	*3.27*	.75	3.25	.65	*2.05*	.99	*2.42*
H. W.	1.17 (.5 to 1.7)	3.19 (3.00 to 3.39)	1.44	*3.49*	1.29	*3.79*	1.39	*3.62*	.68	*2.62*
J. K.	1.14 (.9 to 1.4)	3.38 (3.10 to 3.94)	.75	*3.19*	.58	*2.27*	.90	*3.31*	.40	*2.65*
D. V.	1.33 (.8 to 1.6)	3.36 (2.98 to 3.58)	2.59	*4.73*	1.84	*3.76*	1.13	*3.18*	.53	*2.53*

In the first column (top) are shown the percentage variation of the extremes from the mean of 4 control cardiac output measurements, and individual measurements of cardiac output follow, according to the time elapsed from the beginning of digitoxin administration. Endogenous creatinine clearances are depicted in the second group of columns. The clearance figures not included in parentheses are considered more accurate than those in parentheses, which are based on plasma creatinines drawn during the earlier periods of each day. The first column of clearance data are for the three eight-hour periods in the control day, and the remainder are arranged according to the time following the first dose of digitoxin. In the last group of columns are the values for urinary sodium. The italicized numbers represent 24 hour sodium excretion, and the remainder cover 8 hour periods corresponding to the more accurate filtration rate measurements. The first column of sodium data depicts the mean of 3 or 4 control days, with the highest and lowest values given to indicate the range of control variation. The remainder of the sodium data are given according to the time period following the beginning of digitoxin administration. Digitoxin was given orally to all subjects on a single day only, the dosage schedule being 1.0 mg. at 8:00 a.m., 0.6 mg. at 12:00 noon, and 0.4 mg. at 5:00 p.m.

observations were made at the beginning of this period. Since the eight hour sodium excretions were more variable than were the 24 hour, the latter are also presented.

In figure 1 it can be seen that there was an average rise in 24 hour urine sodium of 3 per cent and 5 per cent, respectively, in the first two 24 hour periods after the beginning of digitoxin ingestion. In only 2 of the 9 subjects was sodium excretion in the first two 24 hour periods of the experiment significantly (more than 10 per cent) less than the average of the controls, and in every subject the sodium excretion during the first two days after digitoxin was greater than on the day immediately preceding the administration of the drug. The findings in subject H. W. (fig. 1) illustrate a striking rise in sodium excretion in the presence of a marked fall in cardiac output during the first 48 hours.

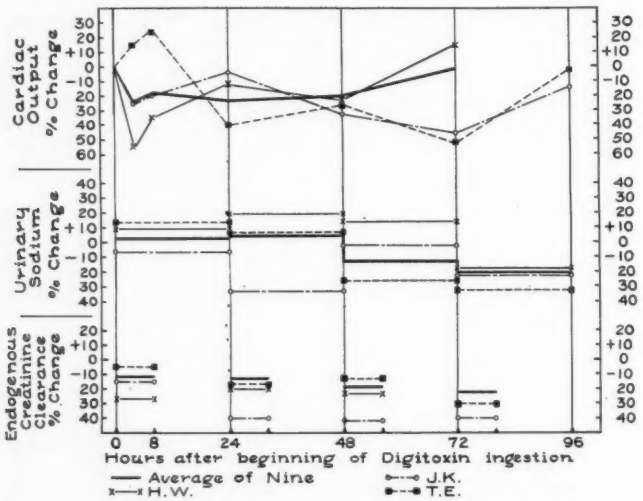

FIG. 1. *The Effect of Digitoxin on Cardiac Output, Urinary Sodium, and Endogenous Creatinine Clearance.* The percentage changes in cardiac output, sodium excretion in the urine, and endogenous creatinine clearance are presented graphically, according to the time having elapsed from the start of digitoxin administration. The control mean in each instance is taken as 0 per cent. The average of all 9 subjects and 3 typical experiments are plotted on the graph. The 48 to 56, and 72 to 80 hour filtration averages are the averages of seven and six measurements, respectively, since in several experiments filtration rate was not measured on each occasion. The average line does not reflect the magnitude of average maximum changes, since the time of maximum change varied in the different subjects; however, it does demonstrate a fall in cardiac output, a fall in filtration rate, and an early rise with a later more marked fall in sodium excretion. The subject, H. W., had a fall in cardiac output in the first 24 hours, and his output remained low until the 72 hour measurement. With this fall in output there was a decrease in filtration rate and, during the first 72 hours, an increase in sodium excretion. Sodium excretion fell in the last 24 hours after cardiac output had returned to normal. The subject, T. E., had an initial rise in cardiac output followed by a fall at 24 hours that continued until the 96 hour determination. His sodium excretion and filtration behaved in a similar manner to those of H. W. Subject J. K., displayed an inverse relationship between cardiac output and sodium excretion. He had a double fall in cardiac output, one in the first 12 hours, and the second at 48 hours. His sodium excretion fell in the period 24 to 48 hours when cardiac output was approaching control level, rose during the second fall in cardiac output, and decreased again as cardiac output finally returned to normal. The filtration rate of J. K. was low throughout the experiment.

In 1 instance (M. G., in the period 16 to 24 hours after beginning digitoxin) a very low sodium excretion (0.37 Gm.) was associated with a very low filtration rate (54 cc. per minute), and with a well marked decline in cardiac output. This was the only occasion in which a striking parallel decline was observed in the three functions. There were numerous

instances in which sodium excretion was unchanged or increased in the presence of reduction of cardiac output.

In 6 of 7 subjects, sodium excretion was decreased on the fourth day after digitalization and in 5 of these 6, cardiac outputs had returned to within or above the control range. The filtration rate often remained low during the third and fourth day after digitalis. The tendency for sodium excretion to fall as the cardiac output returned to normal, and while filtration rate remained low, is illustrated in figure 1 by subject J. K. This subject exhibited a trend toward a reciprocal relationship between cardiac output and sodium excretion.

There was no change in blood pressure except for a slight widening of the pulse pressure in the first 24 to 36 hours. In another study[24] data concerning the effects of digitalis on peripheral resistance and on other hemodynamic functions will be presented. Here, it is sufficient to note that when cardiac output was low, peripheral resistance was increased. If it is assumed that the renal circulation participated in the general increase in peripheral resistance, then renal blood flow was probably diminished to a greater degree than was filtration rate.

Potassium excretion in the urine measured over 24 hour periods was not significantly altered, and there was no correlation between sodium and potassium (table 2). Serum potassium levels measured on the day following digitalis administration were within normal limits.

No significant changes in weight were noted during the experiments.

TABLE 2.—*Comparison between Sodium and Potassium Excretion following Oral Digitoxin.*

Subject		Control Average and Range	Hours after Beginning of Digitoxin			
			0.24	24–48	48–72	72–96
M. G.	Na	3.33 (3.28–3.25)	3.30	3.21	3.44	
	K	3.24 (2.58–3.71)	3.54	3.44	3.28	
J. B.	Na	3.24 (2.94–3.64)	3.68	3.40	2.80	
	K	3.86 (3.39–4.43)	3.83	3.38	5.94	
J. M.	Na	3.96 (25.9–5.52)	2.79	3.56	2.77	2.44
	K	2.59 (2.15–2.86)	3.08	2.61	2.21	2.30
C. C.	Na	3.31 (2.25–4.45)	3.15	5.12	2.42	3.58
	K	3.04 (1.04–4.17)	3.71	2.95	2.34	2.81
T. E.	Na	3.71 (3.24–4.18)	4.13	4.01	2.73	2.58
	K	3.34 (2.88–3.77)	3.05	3.50	3.77	3.22
R. C.	Na	3.45 (3.15–3.81)	3.27	3.25	2.05	2.42
	K	3.24 (2.95–3.40)	3.20	3.91	3.04	3.59
H. W.	Na	3.19 (3.00–3.39)	3.49	3.79	3.62	2.62
	K	1.99 (1.74–2.23)	3.10	3.03	2.64	2.04
J. K.	Na	3.38 (3.10–3.94)	3.19	2.27	3.31	2.65
	K	1.99 (1.51–2.28)	2.44	2.19	2.81	2.66
D. V.	Na	3.38 (3.10–3.94)	4.73	3.76	3.18	2.53
	K	2.83 (2.55–3.08)	3.45	2.93	3.08	2.98

The average 24 hour control excretion and range of control variation for both sodium and potassium are given, one above the other, for each subject. There follow the 24 hour excretions according to the time after the beginning of digitoxin administration. There was no significant consistent change in potassium excretion, nor any correlation between sodium and potassium excretion. The subjects were on a constant sodium diet, but no attempt was made to keep potassium intake constant.

DISCUSSION

During the first two days after digitalization, the apparent cardiac output declined markedly, and the filtration rate was slightly diminished. At the same time there was either no change or an increase in sodium excretion. Thus it would appear that there is no necessary parallelism between these functions in normal subjects. However, in the only instance in which an extreme decline in filtration rate occurred there was a well marked decrease in sodium excretion.

During the second 48 hour period, as cardiac output returned to normal, sodium excretion

declined, while glomerular filtration rate tended to remain low. From the average changes shown in figure 1, it is apparent that the increase in sodium excretion in the first 48 hours was of smaller magnitude than the decline in the second 48 hours. It is not likely, therefore, that the later decline was entirely the result of sodium depletion consequent to the initial increase in excretion.

One possible explanation of the late decline in sodium excretion is that a lowering of cardiac output caused such a decrease but only after a lag of 24 to 48 hours. Another possible explanation is as follows:

There is general agreement[17-19] that digitalis causes decline in circulating blood volume. The mechanism responsible for this is unknown. There is evidence, which will be reviewed in another publication,[24] that the drug causes venoconstriction. If this occurs, the immediate effect would be increased cardiac filling and output, while the persistent effect would be redistribution of blood away from the heart and great veins to the capillaries, and possibly to storage reservoirs. Such a peripheral plethora might lead to increase in blood destruction, such as occurs in normal subjects after transfusion.[31]

If other factors remained equal, venous constriction would tend to elevate capillary surface area and pressure, and to cause increased transudation. Recent studies,[20, 21] indicating that digitalis causes increase in extracellular fluid volume and concomitant decline in blood volume in normal subjects, are in accord with such an interpretation.

It seems likely, therefore, that in normal subjects digitalis causes redistribution of blood with increased volume in certain peripheral areas, and at the same time causes increase in extravascular extracellular fluid volume. If, as is uncertain, these changes affect the intracranial tissues, the directional effects would be similar to those produced by compression of the neck or by changing from the sitting to the recumbent posture. These procedures cause well marked increment in sodium excretion.[11, 12] Five of our 9 subjects studied with digitalis, likewise showed a tendency toward an initial rise in sodium excretion. The inconsistency of this increase would suggest that other, unknown, factors were also concerned.

As the effects of the drug began to wane cardiac output increased, and at the same time sodium excretion declined. Possibly this can be ascribed to a reversal of the previous sequence, with disappearance of venous constriction and movement of extracellular fluid from the extravascular to the intravascular compartment. The findings previously reported[11-13] are readily interpreted by the assumption that alterations in intracranial extracellular fluid volume affect sodium excretion. The same assumption would account for the initial rise and the subsequent decline in sodium output, as observed in the present study.

The failure of potassium to vary in a reciprocal manner with sodium could be interpreted as suggesting that the adrenal cortex does not play a major role in these mechanisms. The lack of consistent changes in urinary potassium excretion seems to indicate that digitalis causes little or no alteration in the volume of the intracellular fluid.

In the attempt to elucidate the relationship between sodium output and alterations in hemodynamics, a number of procedures have been employed in the present and preceding studies.[11-13] The findings are summarized in table 3. They reveal no tendency toward a consistent relationship between sodium excretion, glomerular filtration, and apparent cardiac output as measured by the electrokymographic method. It is, therefore, unlikely that in normal subjects either cardiac output or glomerular filtration is of major significance in the regulation of sodium excretion.

Such a conclusion is not contrary to the concept of a homeostatic mechanism, set into play by hemodynamic factors and serving to conserve sodium. On the contrary, the data appear to support such a concept but to point toward alterations in the volume and distribution of body fluids rather than changes in cardiac output as the initiating mechanism. All of the findings can be explained by the assumption of a volume regulating mechanism brought into play by deficit of extracellular fluid within the cranial cavity, and serving to restore extracellular fluid volume by causing renal conserva-

tion of sodium. In the absence of methods of measuring cerebral fluid volumes, the hypothesis cannot be subjected to direct test. In any case, it is clear that this postulated mechanism is only one of several factors concerned in the regulation of sodium excretion. Whether it is of any significance in disease is as yet uncertain, and will be the subject of future investigation.

are compatible with the idea that a homeostatic mechanism serving to conserve sodium exists, and that this mechanism is initiated by alterations in the volume and/or distribution of body fluids.

TABLE 3.—*Summary of Effects of Various Procedures on Sodium Excretion, Cardiac Output and Glomerular Filtration of Normal Subjects.*

Procedure		Directional Change			
		Cardiac output	Glomerular filtration	Sodium excretion	Remarks
Change from recumbent to sitting position		−−	0	−−−	
Compression of neck of sitting subjects		0	0	++	Compression of neck of recumbent subjects had little effect
Venesection (2.5 cc. per Kg.)	Neck not compressed	0	0	−−	
Sitting	Neck compressed	0	0	+	
Venesection (9 cc. per Kg.)	Neck not compressed	0	−	−−−	
Recumbent	Neck compressed	0	−	−−−	
Recumbent	Neck compressed	0	−	−−−	
Digitoxin (2.0 mg. in 9 hours)	Initial 2 days	−−−	−	+ or 0	Period of maximal action
	Subsequent period	+++	−−	−−	Cardiac output returning to initial level

SUMMARY

Healthy young men were given 0.2 mg. digitoxin in divided doses over a nine hour period.

During the initial 48 hours after the drug, the excretion of sodium increased or remained unchanged. At the same time creatinine clearance was slightly decreased and the apparent cardiac output (electrokymographic method) diminished markedly. This was followed by a period during which the cardiac output returned to the control level, and as this occurred sodium excretion declined. Creatinine clearance was usually still decreased at this time.

The results are considered to constitute evidence against the concept that decline in cardiac output leads to sodium retention. They

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Studies of Tissue Response to Injections of Enzymes

V. Development of Subcutaneous Nodular Masses, and Plasma and Tissue Hexosamine Changes Following Subcutaneous Injection of Streptokinase

By SAMUEL T. SCHLAMOWITZ, M.D., AND ARTHUR C. DEGRAFF, M.D.

The presence of proteolytic enzymes in blood has been known for a long time. A variety of methods and agents have been employed to activate these enzymes. Among these, is streptokinase, a bacterial kinase obtained from the hemolytic streptococcus. The subcutaneous "nodules" and significant hexosamine alterations which occurred following the single subcutaneous inoculation of crude streptokinase, resembled those obtained with partially purified streptokinase and with trypsin-(crude and crystalline). Although it is possible that the results obtained with streptokinase were due to the direct conversion of the proteolytic enzyme to its active form, and that changes noted with trypsin were due to the nullification of the inhibitor with the concomitant liberation of the free and active enzyme, it is also very possible that both trypsin and streptokinase give rise to the liberation of a tissue activator, which in turn catalyzes the transformation of the proteolytic enzyme to its active form.

IN 1893 Dastre[1] noted that serum possesses proteolytic activity. The observation of Delezenne and Pozerski[2] that serum treated with chloroform exhibited proteolytic activity has been repeatedly confirmed.[3-6] A variety of agents and methods have been employed to activate the serum proteolytic enzymes.[7-10] Christensen and MacLeod,[5] Christensen[11] and Ratnoff[12, 13] have demonstrated the conversion of plasminogen to plasmin, by means of the bacterial enzyme, streptokinase. Astrup and Permin[14] demonstrated the activation of the serum proteolytic enzymes by means of a tissue kinase, "cytofibrinokinase," present in tissue washings of cells from various organs. The presence of an activator of the proteolytic enzymes, within the stroma of human erythrocytes, has been reported by Permin.[15] In addition to confirming this observation, Tagnon[16, 17] demonstrated the presence of this activator in a particular fraction of mammalian tissue extract, and found the properties of the activator "to be compatible with the hypothesis that the activator is a kinase acting on the substrate plasminogen to transform it to plasmin."[16, 17] Ungar and Mist[18] have reported the activation of the serum proteolytic enzymes of guinea pigs by means of specific antigen, peptone and certain polysaccharides among which were hyaluronic acid and chondroitin sulfuric acid.

This study was undertaken to ascertain whether the results previously obtained with partially purified streptokinase[19] could be confirmed. It relates the microscopic[20] and macroscopic tissue changes and chemical changes resulting from the subcutaneous injection of crude streptokinase in rabbits. It also affords an opportunity to compare these results with those noted following the subcutaneous injection of trypsin.[21, 22]

MATERIALS AND METHODS

Nine young male albino rabbits* were employed in this study. The animals fulfilled the criteria set forth in the previous studies[21, 22] with regard to age, weight, and clinical status. The methods for

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* The limited supply of streptokinase was sufficient for the study of only 9 animals.

the measurements of the local lesions, enzymatic activity, plasma and tissue hexosamine, and statistical analysis previously described[21, 22] were again employed in this study.

The untreated animals used in the previous studies[20–22] served as controls, and the results obtained in this study were compared with those found in the animals treated with partially purified streptokinase,[19] and trypsin.[21, 22]

firm, nontender, nonerythematous mass appeared at each of the sites in each test animal (table 1). These subcutaneous masses ("nodules") progressively enlarged to attain their maximum in 9 to 14 days, and then slowly regressed. However, at the end of the 30 day experimental period, the "nodules" were still detectable. No conventional signs of inflamma-

TABLE 1.—*The Relation between the Occurrence, Size of the Subcutaneous Mass and Time after A Single Subcutaneous Injection of Streptokinase.*

Key to Nodular Size														
Symbol	Measurements (mm.)													
	Length	Width	Height			Length	Width	Height						
0	0	0	0	through		0	0	0						
±	1	1	1	through		2	2	2						
+	3	3	2	through		5	5	2						
2+	6	6	3	through		8	8	4						
3+	9	9	4	through		11	11	4						
4+	12	12	5	or over = maximum nodules since observed $22 \times 22 \times 12$										

Inoculant	Rabbit Number	Days Postinoculation												
		1	2	3	5	7	9	12	14	16	18	21	24	28
Crude Streptokinase	69	0												
	64	0	0	+										
	66	0	±	3+	3+									
	65	0	±	2+	3+	4+								
	67	0	±	+	3+	3+	4+							
	802	0	±	+	+	2+	4+	4+	4+					
	63	0	±	+	2+	3+	4+	4+	4+	4+	4+	3+		
	68	0	±	2+	3+	4+	4+	4+	4+	4+	4+	3+	3+	2+

Streptokinase.† Crude streptokinase made up in a phosphate buffered saline solution (*p*H 7.4) was prepared so that 1 ml. of the solution contained 10,000 units of streptokinase.

PROCEDURE AND RESULTS

A single injection of 1 ml. of crude streptokinase solution containing 10,000 units was introduced subcutaneously into the shaved area of the plantar surface of each hind leg of each of the 9 rabbits. This area of inoculation is analogous to the human heel region. Within three to five days post inoculation, a distinct, tion, suppuration, necrosis or fixation of tissue, attended the developmental course of these nodular masses.

Within 24 hours after the single subcutaneous inoculation of 10,000 units (1 ml.) of crude streptokinase, a significant elevation of the tissue hexosamine occurred at each injection site. This significant tissue hexosamine elevation at the injection sites and the "nodules" persisted throughout the entire 30 day study period (table 2, fig. 1).

Tissues, both close to the injection sites, as the tendons of Achilles, and distant from the injection sites, as the skin covering the quadriceps femoralis, failed to exhibit any significant alteration (table 2).

The plasma hexosamine became significantly

† Crude streptokinase was generously contributed by Drs. MacLeod and Christensen, Department of Microbiology, New York University-Bellevue Medical Center, New York, New York.

TABLE 2.—*Comparison of Mean Hexosamine Content* of the Injection Sites, "Nodules," Skin,† Tendon,‡ and Plasma following a Single Subcutaneous Injection of Streptokinase with That following a Single Subcutaneous Injection of Trypsin.§*

Inoculant	Number of Animals Examined	Mean	σ	t
Injection Sites and "Nodules"				
Untreated	27	5.16	±0.66	
P.P.S.	7	6.63	±0.39	7.24
C.S.	8	7.08	±1.19	3.95
Cryst. Trypsin	12	7.47	±0.85	8.02
Crude Trypsin	11	7.31	±1.73	3.83
Skin†				
Untreated	27	4.14	±1.04	
P.P.S.	7	4.33	±0.47	0.64
C.S.	8	4.39	±0.56	0.85
Cryst. Trypsin	12	4.56	±0.57	1.19
Crude Trypsin	10	4.31	±0.92	0.56
Tendon‡				
Untreated	30	4.13	±0.76	
P.P.S.	7	4.15	±0.57	0.07
C.S.	8	4.38	±0.89	0.67
Cryst. Trypsin	12	4.14	±0.56	1.23
Crude Trypsin	10	4.45	±0.90	0.94
Plasma				
Untreated	30	51.4	±6.80	
P.P.S.	7	85.4	±6.90	11.3
C.S.	8	84.0	±9.84	8.3
Cryst. Trypsin	10	67.9	±7.53	6.39
Crude Trypsin	12	77.5	±12.80	4.73

* The plasma hexosamine is expressed as mg. hexosamine per 100 ml. plasma. All other values are expressed as mg. per Gm. dry tissue, and cover the entire study period.

† Skin covering the quadriceps fermoralis—a site distant from the injection site.

‡ Tendon of Achilles—subjacent to the injection sites.

§ The values for the trypsin have been reported in *Circulation* **1**: 819–843, 1950.

P.P.S.: Partially Purified Streptokinase

C.S.: Crude Streptokinase

elevated 24 hours after the subcutaneous introduction of streptokinase and remained so throughout the 30 day period of observation (table 2, fig. 2). A secondary rise was found to occur between the tenth and twenty-fourth days post inoculation (fig. 2).

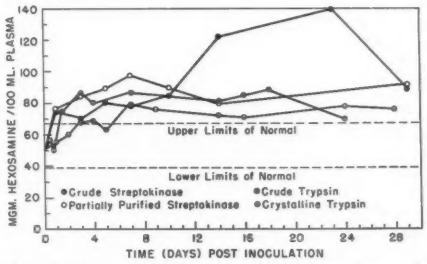

FIG. 1. Comparison of tissue hexosamine values following a single subcutaneous injection of crude and partially purified streptokinase with those following crude and crystalline trypsin.[22]

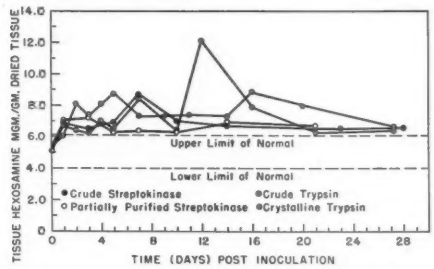

FIG. 2. Comparison of plasma hexosamine values following a single subcutaneous injection of crude and partially purified streptokinase with those following crude and crystalline trypsin.[22]

DISCUSSION

Macroscopically, the subcutaneous masses which developed at the sites of the subcutaneously inoculated crude streptokinase, closely resembled those which occurred following the single subcutaneous injection of partially purified streptokinase[19] and following the single subcutaneous injection of crude or crystalline trypsin.[21, 22] The developmental course of these firm, nontender, non-necrotic, nodular masses, seems to occupy a position intermediate between that caused by the partially purified streptokinase and crystalline trypsin. This is evidenced by the fact that in the animals treated with the partially purified streptokinase, the "nodules" were macroscopically detectable within three to five days;[19] in the trypsin treated group, four to eight days[21, 22] were necessary for the appearance of the "nodules". The subcutaneous nodular masses, which developed following the single subcutaneous inoculation of crude streptokinase attained their maximum size in 10 to 18 days, whereas

those in the partially purified group required 12 to 16 days[19] and those in the trypsin series, 12 to 18 days.[21, 22]

The significant elevation of the hexosamine content of the injection sites and "nodules" which occurred soon (24 hours) after the subcutaneous introduction of the crude streptokinase, closely resembled that which occurred in the series treated with partially purified streptokinase (table 2, fig. 1).[19] In addition, the results obtained with crude and partially purified streptokinase closely resembled those noted in animals which received crude and crystalline trypsin (figs. 1 and 2, table 2). It is obvious that the insignificant amount of hexosamine present in the inoculating dose of the crude streptokinase (table 3) preparation,

TABLE 3.—*Comparison of the Hexosamine Content of the Various Inoculants**

Inoculant	Hexosamine Content
4.2% Crude Trypsin Solution	0.007
1.0% Crystalline Trypsin Solution	0.003
Crude Streptokinase (10,000 units)	0.005
Partially Purified Streptokinase (10,000 units)	0.003

* Expressed as mg. of hexosamine per ml. solution of the inoculant, which is the exact amount of hexosamine introduced via the injection.

could hardly account for the significant hexosamine values obtained.

The presence of proteolytic enzymes in blood have been known for a long time.[1] Likewise, it has been known for some time that treating plasma with chloroform, results in the production of proteolytic activity.[2-6] This is due to the abolition of the plasma inhibitor and activation of the enzymes takes place, presumably by autocatalysis.[5]

Such activation occurs when the proteolytic enzyme plasmin, (which is normally present in plasma in an inactive form called plasminogen) is shaken with chloroform.[6, 17] However, this type of activation is a slow process.[3] Streptokinase, in contrast, catalyzes the transformation of plasminogen to plasmin rapidly.[17]

Thus, as with partially purified streptokinase the inoculating dose of crude streptokinase was considered sufficient not only to overcome the high antiprotease titer present in the rabbits,[6, 24] but to insure an excess.

Although it is tempting to hypothesize that the tissue (macroscopic and microscopic)[20] and chemical changes noted in the studies with the streptokinase preparations were due to the plasmin resulting from the conversion of plasminogen, one must keep in mind that these preparations contain desoxyribonuclease,[5, 6] and its exact role must first be clarified.

It is conceivable that the hexosamine and histologic alterations obtained with trypsin were due to the nullification of the effects of the plasma inhibitor, with the resultant liberation of free and active proteolytic enzyme. The fact that the inhibitor of plasmin is probably identical with plasma antitrypsin[17] and that similar hexosamine and histologic changes were obtained with both trypsin and streptokinase would seem to suggest that there may be some relationship between trypsin and plasmin.

Attractive as these possibilities may be, a third consideration which must not be forgotten is that these substances (trypsin and streptokinase), by their subcutaneous introduction, give rise to the liberation of a tissue activator, identical or similar to those identified by Astrup,[14] Permin,[15] Tagnon,[16, 17] and Unger,[18] which in turn causes the transformation of the inactive plasma proteolytic enzyme (plasminogen) to plasmin.

It is very possible that all of the above factors are simultaneously or successively involved.

SUMMARY

1. Subcutaneous "nodules" which macroscopically resembled those obtained with a single subcutaneous injection of partially purified streptokinase and/or trypsin, developed on the plantar aspect of each of the hind legs of each of the test rabbits in three to five days following the single subcutaneous inoculation of crude streptokinase. As with those animals in the series treated with trypsin and partially purified streptokinase, no erythema, tenderness, eschar, necrosis, slough, breakdown or fixation occurred.

2. The nodular masses increased to a maximum and then regressed. The nodular masses were still present, however, at the termination of the 30 day experimental period.

3. The significant increase in the hexosamine content of tissue at the injection sites and in the "nodules," which occurred within 24 hours of the single subcutaneous injection of crude streptokinase, persisted throughout the entire experimental period.

4. The plasma hexosamine was significantly increased within 24 hours post inoculation and remained so throughout the entire period of study.

5. The results obtained not only closely resemble those noted in rabbits treated with the partially purified streptokinase, but also in the animals treated with trypsin.

6. The histologic and hexosamine changes noted in these studies may be the result of either one or a combination of the following mechanisms: (a) the liberation of the proteolytic enzyme from its inhibitor (antitrypsin) by trypsin; (b) the direct transformation of the enzyme from its inactive state, plasminogen, to its active form plasmin, by streptokinase; or (c) the conversion of the inactive form, plasminogen, to its active state, plasmin, by a tissue activator liberated or increased in amount by the action of these inoculants.

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Studies on the Spread of Excitation through the Ventricular Myocardium

By Raymond D. Pruitt, M.D., Hiram E. Essex, Ph.D., and Howard B. Burchell, M.D.

The speed at which the excitatory process spreads through a certain segment of the myocardial syncytium depends upon the orientation of the fibers in that segment to each other and to the point of origin of excitation. Spread down a strip of fibers of which the long axis is parallel to the long axis of the strip is rapid as compared with spread down a strip in which the fibers run at a right angle to the long axis of the strip. Endocardial activation is rapid, not because of the presence of Purkinje fibers, but because the subendocardial bands of myocardium form a network through which excitation can move rapidly along the long axis of the fibers. Spread across the septum in bundle-branch block and across the free wall of the left ventricle in the normally activated heart is slow because excitation is moving through fibers the long axis of which is prependicular to the advancing wave of excitation.

THE EXISTENCE of a differential in the speed at which the excitation process spreads through the myocardium of the mammalian ventricles rests on a substantial foundation. The phenomenon of bundle-branch block attests to a slow rate of transmission across the interventricular septum. The work of Lewis and Rothschild[1] indicated equally slow transmission through the left ventricular wall in contrast to rapid spread through the subendocardial tissues. To account for these variable speeds of transmission the property of propagating the excitation process at a relatively rapid rate was ascribed to the Purkinje network. In recent years, the existence in the human and in the canine heart of a network of fibers sufficiently distinct morphologically to merit the name of a Purkinje system has been denied.[2] However, rapid excitation of the subendocardial tissues is a physiologic phenomenon so well established that its existence is not subject to challenge even if a system of fibers specialized to that accomplishment cannot be demonstrated.

Part I. The Effects of Endocardial Injury on the Spread of the Excitation Process

In 1945 Pruitt, Barnes and Essex[3] reported certain experimental results which led them to conclude that widespread injury to the endocardium and subendocardial myocardium of the left ventricle in dogs produced electrocardiographic changes indicative of an alteration in the course but not in the speed of excitation of the ventricular myocardium. An exception to this general rule was encountered in an injury involving the interventricular septum at a site just below the aortic valve. These experiences led to the generalization that in the left ventricle "a lesion high on the septum apparently not only is attended by widening of the QRS complex but also it is the only lesion likely to produce this effect." In this conclusion no exception was taken to that large and convincing body of evidence which supports the existence in the upper part of the septum of a localized conducting pathway which can be interrupted by disease processes or by traumatizing procedures. But the suggestion that significant widening of the QRS complex can be produced in an acute experiment only by a lesion in this upper septal region is a departure from the commonly accepted view. If rapid subendocardial excitation is mediated by the Purkinje fibers, then destruction of these fibers should be feasible and arborization block should be the consequence. In the years which followed the publication of this initial study on subendocardial injury, the authors came to recognize the apparent inconsistency between their observations and data derived from other lines of investigation.

Interest in the problem was stimulated by the observation of certain bizarre complexes which appeared within a few minutes after

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ligation of a large branch of a coronary artery in the dog (fig. 1). A hypothesis was advanced that these complexes might be related to arborization block which was a transient phenomenon, disappearing as injury extended from endocardium toward epicardium. When the zone of injury reached the epicardium, blocking of excitation at the margins of the lesion occurred and the bizarre complexes ascribed to anomalous excitation of islands of viable cells disappeared, to be replaced by complexes regarded as typical of an acute myocardial injury. If this explanation was valid, then reproduction of these complexes should be accomplished by a diffuse severe endocardial injury.

Repeated encounters with complexes of a similar kind in certain patients in the acute phase of myocardial infarction or pulmonary embolism heightened interest concerning the origin of such deflections.[4]

In attempting to reconcile these observations with earlier experiences with subendocardial injury, it was postulated that the lesions accomplished in those initial experiments were diffuse but may not have been sufficiently severe to produce complete interruption of spread through all parts of a network of fibers so intricate as the Purkinje system. The conviction that a lesion sufficient to destroy that system need not extend far beneath the endocardium was maintained by the following consideration: if spread of excitation through the Purkinje fibers is at a rapid rate whereas endocardial-epicardial spread is slow, then the specialized conducting tissue must be confined to the tissues immediately adjacent to the endocardium.

Method

Since mechanical trauma had failed to accomplish the predicated effects on spread of excitation, an attempt was made to develop a preparation wherein necrotizing agents could be applied directly to the ventricular endocardium while the remainder of the myocardium was nourished by a coronary system perfused with a solution of physiologic nature. This, so it was reasoned, would insure production of a lesion at once diffuse, severe and limited to the subendocardium. Strong as was the bias toward studies carried out on a heart in situ, devising a simple preparation fulfilling the requirements of the experiment did not appear feasible. Attention was turned, therefore, to the isolated perfused canine heart preparation as described originally by Langendorff. In this preparation the coronary system is profused under pressure by fluid introduced through the aorta. Competently functioning aortic valves prevent reflux of any large amounts of the perfusate into the left ventricular cavity, and such small quantities as do enter the cavity can be aspirated through a tube introduced by way of the auriculoventricular orifice. The left ventricular cavity, once freed of fluid, will

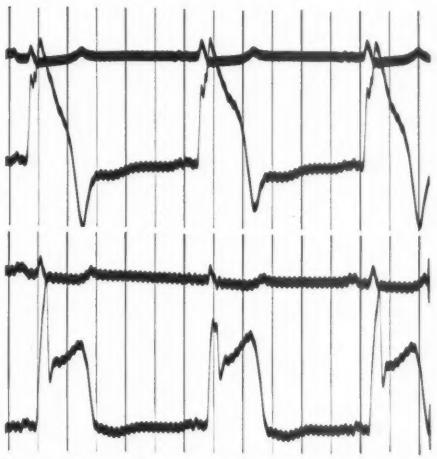

FIG. 1. Two strips recorded on a Sanborn Tribeam at 75 mm. per second are reproduced. In both the upper and lower strips the upper complexes are standard limb lead III. The lower complexes in the upper strip were recorded in a direct lead from the epicardium of a canine left ventricle, at a point supplied by a ligated branch of the anterior descending coronary artery. These complexes appeared about five minutes after the vessel was occluded. In the lower strip, the lower complexes were recorded in the same manner as in the upper strip. An interval of two minutes elapsed between the two records. Lead III was recorded at normal sensitivity (1 cm. = 1 mv.). Direct leads from the surface of the heart were recorded at approximately one-fifth normal sensitivity (N/5).

remain so for a time sufficient to permit any necrotizing agent placed in the cavity to exert its effect before significant dilution occurs. Cannulation of the pulmonary artery permits diversion from the left ventricular region of perfusate expelled by the right ventricle. The single experiment in which cocaine was introduced into the right ventricle admittedly was imperfect from the technical point of view, but certain adjustments were made and will be described in connection with the results of that particular experiment.

Electrocardiographic Technic. A Sanborn Tribeam

electrocardiograph was used to obtain two simultaneous records on the same strip of paper. One terminal of each circuit was attached to an electrode consisting of an enameled copper wire 1.2 mm. thick from the tip of which the enamel had been removed. This tip was then immersed in the perfusing fluid, which as it escaped from the heart was collected in a glass dish. The distance between the tip of this electrode and the point at which the heart made contact with the collected perfusing fluid was approximately 15 cm. The lower one-third to one-half of the ventricular surfaces was submerged in this fluid. The other terminal of each galvanometer circuit was attached to an electrode placed at some point on the epicardium or in one of the ventricular cavities. These electrodes were made of a fine copper wire one end of which was fixed to a small piece of cotton. The wire was then drawn through a piece of polythene tubing, leaving only the tip of the cotton wick exposed. Only this wick touched the epicardium or endocardium. These exploring electrodes were attached to that terminal of the galvanometer at which relative positivity produced an upward deflection.

The sensitivity at which the electrocardiograph was operated was not always the same. Hence in each set of records the sensitivity is indicated.

Results

Ample evidence exists that 0.1 molar solution of potassium chloride applied to the epicardium produces changes which are reflected in the electrocardiogram in marked displacement of the RS-T segment; except for their reversible character, these electrocardiographic changes are like those induced by traumatizing the epicardium by any one of a number of other methods. Hence 0.1 molar solution of potassium chloride appeared to be a solution suitable to the production of a diffuse subendocardial lesion. When a solution of this concentration failed to evoke changes suggestive of arborization block, stronger solutions were introduced. In figure 2 are reproduced the complexes which developed when crystals of potassium chloride were sprinkled in the cavity of the left ventricle. The changes encountered in this instance differed in no significant way from those which developed in earlier experiments in which solutions of potassium chloride of varying concentrations were placed in the cavity. The essential characteristics of these complexes may be summarized as follows. In the leads from the left ventricular cavity, the QS deflection of the control record was replaced by an essentially monophasic ventricular complex consisting of a tall R wave

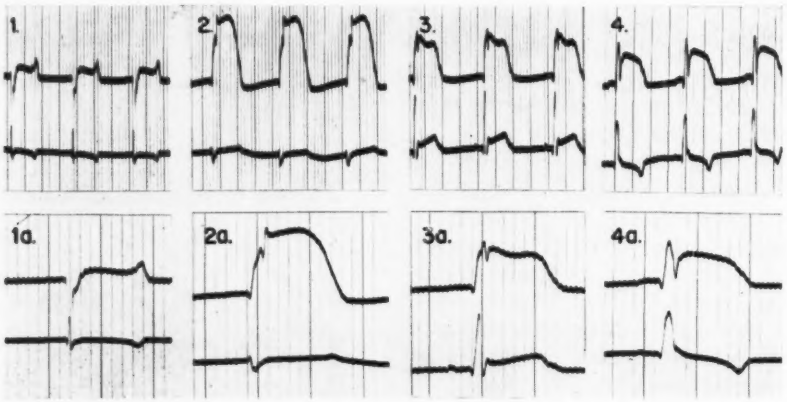

FIG. 2. Records labeled with a numeral only were obtained at a camera speed of 25 mm. per second. Records labeled with a numeral and letter *a* were obtained at a camera speed of 75 mm. per second. 1 and 1*a*. Upper complexes were recorded with exploring electrode in left ventricular cavity and lower complexes with exploring electrode on the anterior surface of the left ventricle. 2 and 2*a*. Records made a few seconds after a saturated solution of potassium chloride had been introduced into the left ventricular cavity. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on anterior surface of right ventricle. 3 and 3*a*. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on lateral surface of left ventricle near base. 4 and 4*a*. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on anterior surface of left ventricle. Sensitivity, upper and lower complexes: N/5.

followed by an S-T segment which is markedly elevated. A shallow Q deflection precedes the R wave. In leads from the left ventricular surface, the changes were not so striking. A shallow Q wave present in the control record persists and is followed by a tall R wave. The total width of the QRS complex increased from approximately 0.03 second to approximately 0.065 second.

Since application of potassium chloride to the endocardial surface did not produce a widening of the QRS complex greater than that which attends bundle branch block, solutions of a more noxious nature were selected for succeeding experiments. Introduction of a saturated solution of silver nitrate and of 80 per cent solution of phenol into the left ventricular cavity was attended by electrocardiographic changes quite similar to those encountered in the experiments with potassium chloride.

Phenol and silver nitrate in the concentrations used in these experiments destroy those cells with which they come in contact. However, the depth of the lesion resulting from application of these substances appears to be approximately 1 mm. An attempt was made, therefore, to find a substance the effects of which would not be so sharply delimited by its own necrotizing action. Potassium chloride reasonably might have been such a substance, but its efficacy appeared to have been disproved by the test of experiment. Cocaine represents a class of substances peculiarly effective in interrupting transmission of excitation along nerve fibers. The possibility existed that it might prove effective in slowing or interrupting the process of myocardial excitation. Solutions of varying concentrations were used, but none proved more effective than that which contained 5 per cent cocaine. In figures 3 and 4 are reproduced electrocardiograms obtained during this series of experiments. The results are of interest in three respects: (1) Changes in the QRS complexes developed in a progressive fashion. The intermediate stages in this evolution are as significant, perhaps, from the standpoint of electrocardiographic theory and its clinical applications as the end results themselves. (2) These QRS changes were unattended by major deviations in the RS-T segment such as occurred in experiments in which noxious agents of other types were used. The restricted nature of the change in the ventricular complex rendered the results simpler and more significant. (3) Heart block of increasing degree developed in this experiment. (See records 5 and 5*a* of figure 4. See also 4 and 4*a* of figure 8.) If the drug exerted its effect on the junctional tissue, there is reason to believe that it would have blocked transmission through any conduction pathways located in the subendocardial tissues.

Figures 4, 5 and 6 contain records from experiments in which an incision was made across the upper portion of the left side of the interventricular septum either before or after introduction of a cocaine solution into the left ventricular cavity. When this incision was made before the cocaine was applied, the complexes recorded in leads from the left ventricular surface and from the left ventricular cavity are of a kind regarded as typical of left bundle-branch block (fig. 5, records 2, 2*a*, 3 and 3*a*). Following the instillation of cocaine into the left ventricular cavity, the QRS complexes recorded in leads from that cavity assumed an essentially monophasic character (fig. 6). However, no appreciable increase occurred in the width of these complexes. When the experiment was conducted in the reverse order, production of the septal lesion had no significant effect on the form of the QRS complexes which had developed after application of cocaine. (See records 11, 12 and 12*a*, figure 4.)

Cocaine in Right Ventricle.—In figures 7 and 8 are reproduced the electrocardiograms recorded in an experiment in which crystals of cocaine were introduced into the right ventricular cavity. Even though the return of perfusing solution through the coronary sinus was diverted, the right ventricular cavity filled with perfusing fluid within a few seconds. Hence, continuous aspiration of fluid from the cavity had to be carried out. Even so, contamination of the epicardial tissues by cocaine-containing fluid may have occurred during some phase of the experiment.

The results of this experiment appear to afford a fairly close counterpart to the findings obtained on traumatization of the left ventric-

ular endocardium. The lead from the right ventricular cavity in the control record shows a tiny upward deflection followed by a deep S wave (fig. 8, 1*a*). After application of cocaine, this complex is supplanted by one in which tiny R and S waves are followed by a tall broad R′ deflection (fig. 8, 2*a*). In the leads from the right ventricular surface, the rS complex of the control record evolved into an rsR complex. The width of the complexes increased from 0.04 second in the control record to 0.08 second in those obtained after instillation of cocaine.

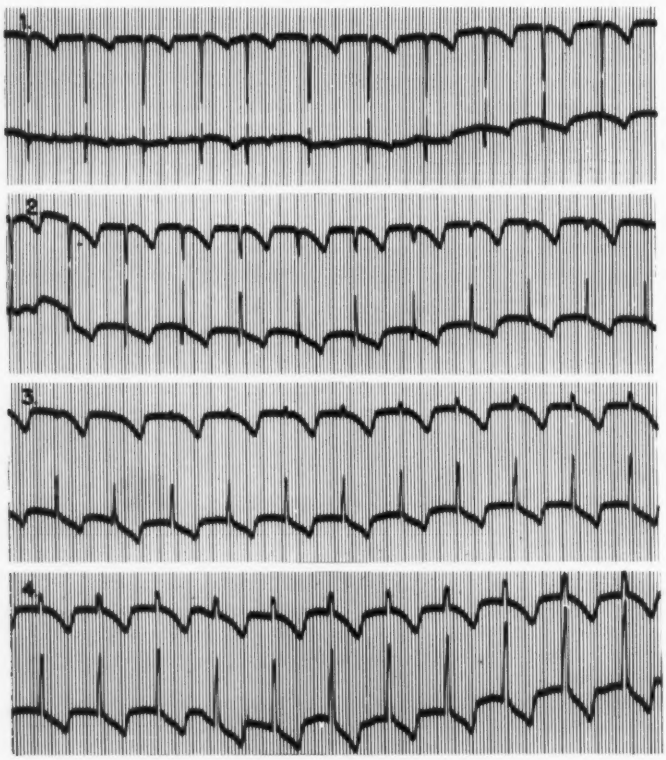

FIG. 3. As the recording of strip 1 began, 5 cc. of a 5 per cent solution of cocaine were introduced into the left ventricular cavity. Strips 2, 3 and 4 represent an uninterrupted record of the changes in form of complexes from a left ventricular cavity lead (above) and a lead from the anterior surface of the left ventricle (below). Sensitivity, upper complexes: N/15; lower complexes: N/7.5.

Comment

The significant features of these results may be summarized as follows:

1. Diffuse endocardial trauma, whether accomplished by instillation of potassium chloride, silver nitrate, phenol or cocaine into the left ventricular cavity, did not produce a greater increase in the width of the QRS complex than commonly attends production of a discrete lesion high on the left side of the interventricular septum. Apparently such injuries did not reduce the speed at which the excitatory process spreads through the left ventricular myocardium. The phenomenon of arborization block was not reproduced by destruction or injury of these endocardial and subendocardial tissues.

2. With impressive consistency, the form of the QRS complexes in leads from the ventricular cavities changed from an essentially

monophasic negative complex to an essentially monophasic positive complex following endocardial injury with any one of the several substances used in these experiments. This change was reduced to its simplest form in the experiments with cocaine, in which segmental shifts were minimal. The recording of such complexes simultaneously from both the endocardial and epicardial aspects of the ventricular wall would appear to indicate that the exploring electrodes placed on either side of that wall bore a similar spatial relationship to the potentials set up during its excitation. Such a relationship could exist if the excitatory process were spreading through the ventricular wall, not from endocardium to epicardium as in the normally activated heart, but in a fashion wherein its front travels in a plane perpendicular to that of the epicardial and endocardial surfaces.

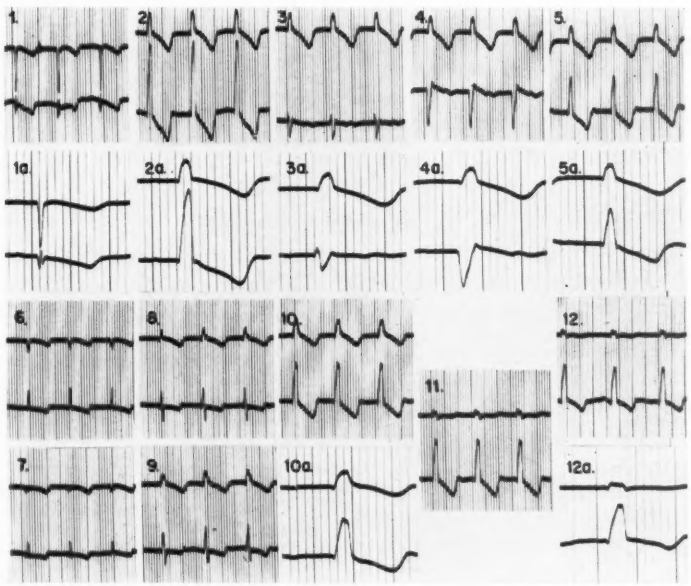

FIG. 4. Additional electrocardiograms recorded in the same experiment as those in figure 3. 1 and 1*a*. Records made immediately before those in figure 3. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on anterior surface of left ventricle. 2 and 2*a*. Records made immediately after those in figure 3. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on anterior surface of left ventricle. 3 and 3*a*. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on surface of right ventricle. 4 and 4*a*. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode in right ventricular cavity. 5 and 5*a*. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on surface of left ventricle. Note that P-R interval in these records is 0.18 second as compared with 0.13 second in control records 1 and 1*a*. 6. Record obtained 20 minutes after 5 and 5*a* and at a time when crystals of cocaine were being sprinkled into the left ventricular cavity. Upper complexes: exploring electrode in left ventricular cavity. Lower complexes: exploring electrode on anterior surface of left ventricle. 7. As for 6, 10 seconds later. 8. As for 7, 10 seconds later. 9. As for 8, 10 seconds later. 10 and 10*a*. As for 9, 10 seconds later. 11. As for 10, but 10 minutes later and immediately before an incision was made across upper portion of ventricular septum just below the aortic valve, so disposed as to interrupt conduction through the left bundle branch. 12 and 12*a*. As for 11, immediately after lesion had been made on septum. Sensitivity, upper complexes: N/10; lower complexes: N/5.

3. Both the failure to produce arborization block and the appearance of complexes para-

doxic for endocardial-epicardial spread suggest that pathways over which ventricular excitation can spread rapidly exist in portions of the wall apart from the tissues immediately beneath the endocardium.

In an attempt to account for these findings, the following hypothesis was proposed. The speed at which the excitation process spreads through a certain segment of the myocardial syncytium depends upon the orientation of the fibers in that segment to each other and to the point of origin of excitation. Spread down a strip of fibers in which the long axis of the fibers is parallel to the long axis of the strip is rapid as compared with spread down a strip in which the fibers run at right angle to the long axis of the strip. Endocardial activation is rapid, not because of the presence of Purkinje fibers, but because the subendocardial bands of myocardium form a network through which excitation can move rapidly along the long axis of the fibers. Spread across the septum in bundle-branch block and across the free wall of the left ventricle in the normally activated heart is slow because excitation is moving through fibers the long axis of which is perpendicular to the advancing wave of excitation.

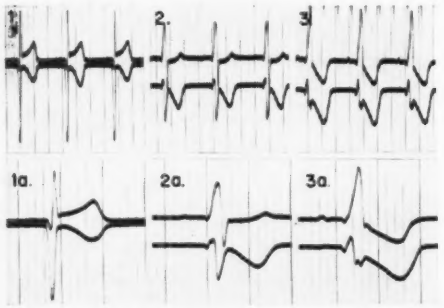

FIG. 5. 1 and 1*a*. Upper complexes: exploring electrode on lateral surface of left ventricle near base. Lower complexes: exploring electrode in left ventricular cavity. 2 and 2*a*. After a lesion had been made across left side of interventricular septum just below aortic valve. Upper complexes: exploring electrode on anterior surface of left ventricle near apex. Lower complexes: exploring electrode in left ventricular cavity near apex. 3 and 3*a*. Upper complexes: exploring electrode on lateral surface of left ventricle near base. Lower complexes: exploring electrode in left ventricular cavity near base. Sensitivity, all leads: N/15. See figure 6 for additional records.

Perhaps the most substantial argument for this hypothesis may be found in a consideration of the structure of the myocardial syncytium; such a study suggests that the course that depolarization must pursue in moving across the bridges between the fibers is much longer than a direct route down the long axis of a single fiber. For a time, the acquisition of other support for this hypothesis appeared uncertain. The experiments to be reported fail to resolve all the limitations imposed on its test-

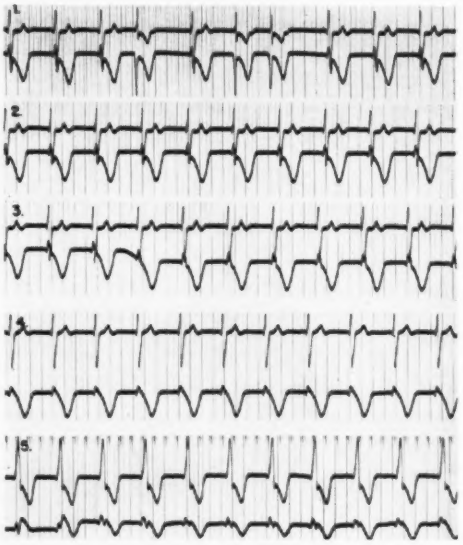

FIG. 6. These electrocardiograms were recorded from the same heart and in immediate sequence to those in figure 5. As the record of strip 1 began, 5 cc. of 5 per cent solution of cocaine were introduced into the left ventricular cavity. Strips 2, 3 and 4 represent an uninterrupted record of the changes in form of complexes in a lead from the anterior surface of the left ventricle near the apex (above) and in a lead from the left ventricular cavity (below). Strip 5 was recorded several minutes later, after crystals of cocaine had been introduced into the left ventricular cavity. The upper row of complexes represents a lead from the lateral aspect of the left ventricle near the base. The lower row was obtained from the left ventricular cavity as the exploring electrode was moved from the apex toward the base of the heart. Sensitivity, all leads: N/15.

ing by the architecture of the heart. The results achieve significance of a degree only when integrated with data already reviewed.

ess entered the strip at its attachment to the ventricular wall. Hence the source of a regularly recurring stimulus was established.

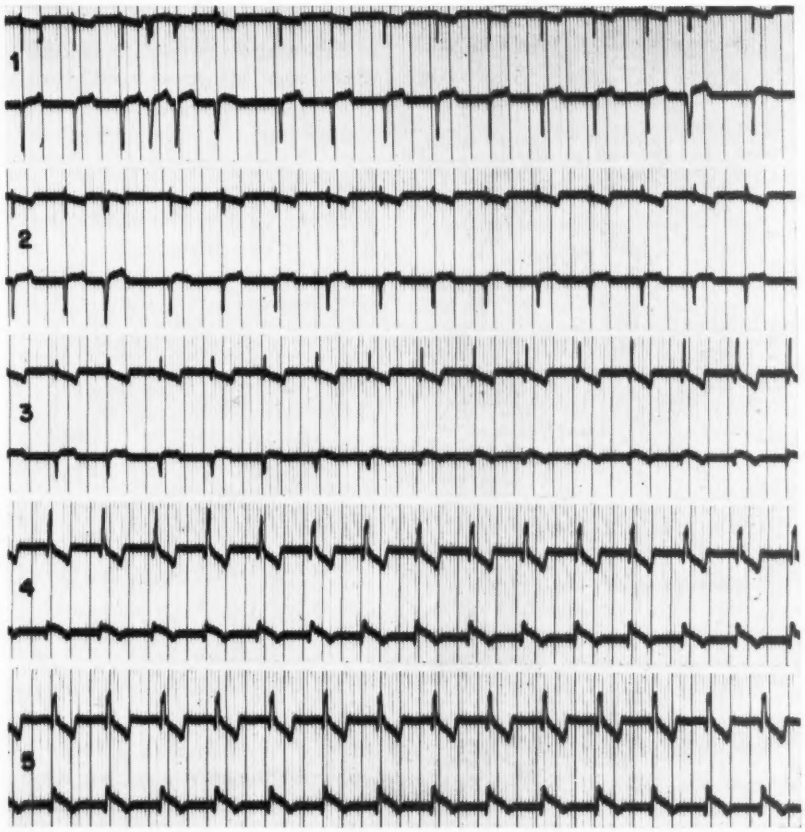

FIG. 7. As the recording of strip 1 began, crystals of cocaine were introduced into the right ventricular cavity. Strips 2, 3, 4 and 5 represent an uninterrupted record of the changes in the form of complexes in a lead from the anterior surface of the right ventricle (above) and from the right ventricular cavity (below). Sensitivity, all leads: N/15. See also figure 8.

PART II. THE SPREAD OF EXCITATION DOWN A STRIP OF MYOCARDIUM

In this series of experiments, the objective was isolation of a strip of the ventricular wall, except for an attachment at one end. Strips of two kinds were desired. In one, the long axis of all or part of the fibers should lie parallel to the long axis of the strip. In the other, the long axis of the fibers should lie at a right angle to the long axis of the strip. The excitatory proc-

In the canine heart a myocardial strip, if it was to remain functioning, had to retain its arterial supply. This requirement was met more readily for strips in which the fibers ran transversely than for those made up of fibers disposed parallel to the long axis of the isolated segment.

Studies were carried out on preparations of two types. In one, a band of superficial fibers was separated from the beating heart in situ. In the other, a "full-thickness" strip of the

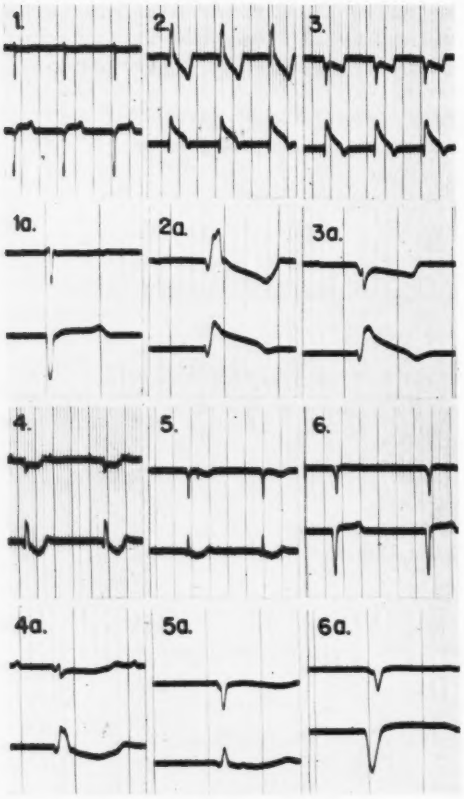

FIG. 8. 1 and 1*a*. Control records. Upper complexes: exploring electrode on anterior surface of right ventricle. Lower complexes: exploring electrode in right ventricular cavity. 2 and 2*a*. Records made immediately after those in figure 7. Upper complexes: exploring electrode on anterior surface of right ventricle. Lower complexes: exploring electrode in right ventricular cavity. 3 and 3*a*. Upper complexes: exploring electrode on anterior surface of left ventricle. Lower complexes: exploring electrode in right ventricular cavity. 4 and 4*a*. Upper complexes: exploring electrode on surface of left ventricle. Lower complexes: exploring electrode on surface of right ventricle. Note 2:1 auriculoventricular block. 5 and 5*a*. Record made 15 minutes later. Upper complexes: exploring electrode in right ventricular cavity. Lower complexes: exploring electrode on epicardial surface of right ventricle. Note decreasing degree of intraventricular block. 6 and 6*a*. Upper complexes as in 5 and 5*a*. Lower complexes: exploring electrode in left ventricular cavity. Sensitivity, all leads: N/15.

left ventricular wall was prepared in an isolated perfused heart. Because of limitations of space and because the results from both types of experiments were essentially the same, only the data from one experiment will be reported. For simplicity of description this experiment will be divided into two parts.

Experiment I, Part I. A segment of the left ventricular wall in which the long axis of the epicardial fibers occupied a position parallel to the long axis of the strip was prepared on an isolated perfused heart (fig. 9, strip I). Both in an earlier experiment with this same preparation and in the present experiment, isolation of the heart and freeing the lateral and distal

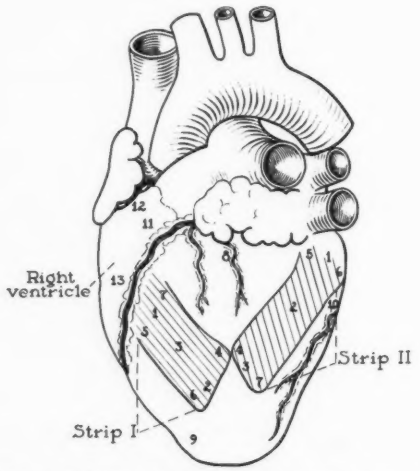

FIG. 9. Diagram of heart, left lateral view, with strips prepared as described in text under experiment I. Strip I is related to part I of that experiment and strip II to part II of that experiment. Electrocardiograms are reproduced in figures 10 and 11.

margins of the strip produced no appreciable widening and only minor alterations in the form of the QRS complexes in unipolar leads from the base and the tip of the strip. Examination of record 5*a* in figure 10 discloses the reason for this. The complexes marked "En. 1" were recorded with the exploring electrode in contact with the endocardium at the base of the strip. These complexes have the simple QS form of a lead from the ventricular cavity. They afford evidence that excitation reached this point very early in electrical systole and in a manner differing little if any from the normal.

The electrocardiographic changes which attended subsequent steps in the experiment are reproduced in figure 10. Except for the lowest row of tracings, the records in the first column were made with the exploring electrodes at the base of the strip. In one lead, the electrode rested on the epicardial surface (Ep. 1) and in the other, on the endocardial surface (En. 1). In the second column appear the records made when the elctrodes were moved to points midway between base and tip of the strip. In the third and final column appear the records obtained when the electrodes occupied positions on the epicardium and endocardium at the tip of the strip. Records 5*a* and 7*a* were made after isolation and perfusion of the heart, but with the endocardial attachment of the strip intact. No tracings were made at this stage from a midpoint on the strip, and record 6 is a standardization. Records 12*a*, 13*a*, and 14*a* were made after the endocardial fibers at the base of the strip had been severed. A striking change occurred in the form of the complexes in the lead from the endocardial surface of the strip just distal to the site of the incision (En. 1). The simple QS deflections of record 5*a* were replaced by complexes in which a small Q wave is followed by a tall R wave. Apparently this endocardial point no longer is activated very early in electrical systole. The complexes in leads from the epicardium at the base of the strip (Ep. 1) changed in form comparatively little. The intrinsic deflection in leads from the epicardial surface at the tip of the strip (record 14*a*, Ep. 2) is delayed approximately 0.03 second as compared with leads from a similar point prior to severing the endocardial attachment (record 7*a*, Ep. 2). A similar delay appeared in the records from the endocardial surface of the tip (record 14*a*, En. 2).

Records 19*a*, 20*a* and 21*a* were made after shearing away the entire endocardial aspect of the strip. Examination of these complexes reveals that they remained essentially unchanged from those obtained from comparable points prior to removal of the endocardial fibers.

The results of this first portion of the experiment indicate that once the early arrival of the excitation process at the endocardial attachment of the strip is interrupted by a simple incision across the base of the strip, further trauma or complete removal of the endocardial tissues does not affect the form of the complexes recorded from the strip. These results are compatible with the view that when the disposition of epicardial fibers parallels the long axis of the strip, excitation moves down them as rapidly as through the underlying endocardial fibers of similar disposition. Such are the results when the long axis of fibers constituting the epicardium of the strip lies parallel to the long axis of the strip.

Before going on to part II of this experiment, attention may be directed to the fact that the lowest row of tracings in figure 10 includes two labeled 16*a*. One of these is made up of complexes from points 7 and 6 on strip I. The other is of particular interest because the complexes from points 1 and 2 were recorded from strip I after part II of the experiment had been completed. The absence of any change in the form of these complexes as compared with complexes recorded from similar points prior to undertaking the second portion of the experiment indicates that the preparation remained in excellent condition throughout this second stage. The exceptionally wide QRS complexes to be seen in part II were not related, therefore, to a failing preparation.

Experiment I, Part II. In part II of this experiment study was made of the consequences of applying to a strip the epicardial fibers of which lay approximately at right angles to the long axis of the strip those same procedures carried out in part I. In figure 9 is reproduced a sketch of the heart in which the location of the two strips and their spatial relationship to each other are indicated. On each strip the course of the epicardial fibers is represented by the parallel lines.

The electrocardiograms recorded in part II are reproduced in figure 11. In each set of tracings, apposite epicardial and endocardial points were explored. Point 1 lay at the base of the strip, point 2, halfway between base and tip of strip, and point 3, at the tip of the strip. Records 1*a*, 2*a* and 3*a* were made immediately after the strip was prepared. Records 6*a*, 7*a* and 8*a* were obtained after the endo-

cardium at the base of the strip was severed from its ventricular attachment. Records 11*a*, 12*a* and 13*a* were made after the endocardial half of the strip had been sheared away.

Certain differences between the electrocardiograms obtained from strip II and those from strip I merit review. These differences are as follows:

1. The intrinsic deflection in complexes derived from the endocardial attachment of strip II to the left ventricle is some 0.03 second delayed as compared with complexes from the endocardial attachment of strip I. Hence delay of that deflection by a comparable interval would be anticipated in complexes recorded from more distally situated points on strip II. Such was the case with respect to complexes derived from all endocardial points up to the stage in the experiment when the endocardial half of the strip was removed (end of row 2 in fig. 11). The delay in onset of the intrinsic deflection was somewhat greater in complexes derived from an epicardial point at the tip of strip II (Ep. 3 in fig. 11). This variation may well have been related to the difference in orientation of epicardial fibers with respect to the strip as a whole.

2. With the exception of the accountable variations noted in the preceding paragraph,

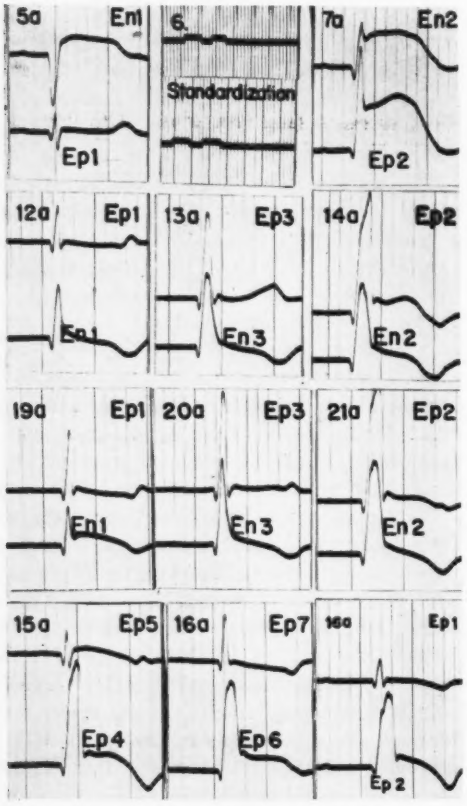

FIG. 10. Electrocardiograms from part I of experiment I. For detailed description, see text. Numerals refer to points on strip I of figure 9. Except for the standardization, all records in the illustration were made at a camera speed of 75 mm. per second. Sensitivity, all leads: N/15.

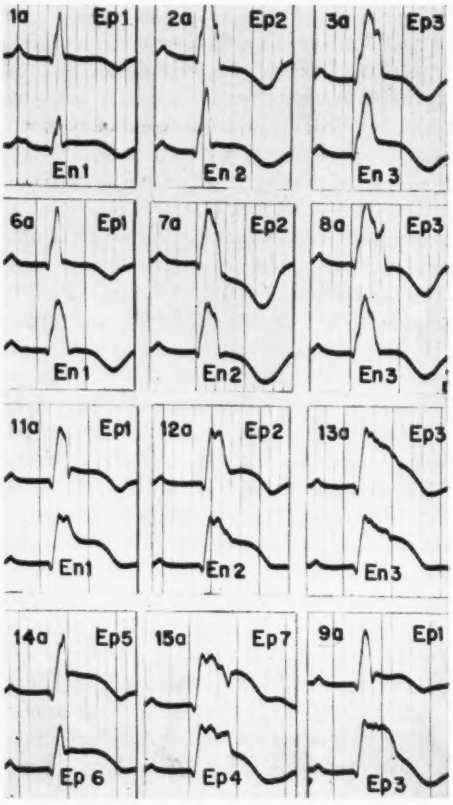

FIG. 11. Electrocardiograms from part II of experiment I. For description see text. Numerals refer to points on strip II of figure 9. All records in this illustration were made at a camera speed of 75 mm. per second. Sensitivity, all leads: N/15.

the complexes recorded from strips I and II were essentially the same up to the stage in the experiment when the endocardial portion of each strip was removed (end of row 2 in fig. 10 and end of row 2 in fig. 11). Removal of the endocardial portion of strip I was attended by no significant changes in the electrocardiograms derived from representative points on that strip. The same measure when applied to strip II was followed by an increase of about 0.04 second in the duration of the QRS complex in a lead from the epicardium at the tip of the strip and of about 0.06 second in the lead from the under surface of the strip at its tip.

Removal of the endocardial portion of the strip appears, therefore, to be the critical measure in distinguishing the responses of strips with contrasting distribution of the epicardial fibers. Examination of strip II disclosed that along its endocardial aspect ran a columna carnea made up of fibers the long axis of which was parallel to the long axis of the strip. If distinction in the performance of strips I and II depended on removal of all longitudinally disposed fibers from one of the strips, then this state was achieved only with removal of the endocardial portion of strip II. Thereupon the predicated delay in the onset of the intrinsic deflection of the QRS complexes developed in complexes recorded from the tip of the strip.

Comment

Discussion of results well may begin with a restatement of that premise which introduced this experimental study: spread of the excitation process through the subendocardial tissues takes place at a speed rapid in comparison with transmission through the remainder of the myocardium. The irrefutable fact supporting this premise is the phenomenon of bundle-branch block. Confirmation is found in the work of Lewis pertaining to the arrival of the excitation process at several points on the epicardial and endocardial surfaces of the ventricles. Calculation of the speed at which the excitation process spread through the myocardial fibers was made on the basis of the time required for its spread across the septum from the endocardium of one ventricle to the endocardium of the other or the interval between excitation of an endocardial point and an apposite point on the epicardium. In either event, a peculiar circumstance pertained; namely, that in order to reach that apposite point excitation must proceed "across the grain" of the fibers composing that portion of the septum or free wall.

In contrast, in spreading from a point high on the septum over the endocardial aspect of a ventricle, the excitation process was proceeding "with the grain" of the myocardial fibers composing the subendocardial tissues. Hence the phenomenon of rapid subendocardial spread may be related not to a peculiar conductivity possessed by the constituent fibers but to a peculiar character of their disposition.

In the light of this proposal, certain experimental and clinical phenomena may be reviewed.

1. *Experimental Subendocardial Injury.* Whether produced in the heart in situ by mechanical means, or in the isolated perfused heart by chemical trauma, widespread subendocardial injury in the left ventricle of the canine heart failed to evoke slowing of ventricular excitation in excess of that which can be accomplished by a small lesion placed high on the left side of the septum. These results are difficult to reconcile with the hypothesis that rapid transmission of excitation is a property of the network of cells confined to the subendocardial tissues. If, however, the thick ridges of subendocardial muscle cells are the medium through which rapid spread of excitation is accomplished, preservation of this function in the face of traumatizing procedures applied in the experiments just cited is understandable.

2. *Bundle-Branch Block.* The results presented and the hypothesis proposed here are not discordant with well-established concepts pertaining to bundle-branch block. The existence in the interventricular septum of the canine heart of relatively small regions, injury to which modifies profoundly the sequence of ventricular excitation and the form of the electrocardiogram, is an established fact. On the other hand, the exact course taken by the excitation process once its normal spread through the bundle branch has been interrupted remains uncertain. This problem may be

approached by a review of ideas pertaining to the course taken by excitation (*a*) in the normally activated heart and (*b*) in the presence of bundle-branch block. The term "homolateral ventricle" will be used to designate the chamber to which the bundle is blocked.

(a) When the heart is normally activated, excitation of the left ventricle begins at a point high on the septum and spreads rapidly over the endocardial surface of that ventricle. The exact course of spread from endocardium to epicardium is not established, but the order is such that an epicardial point is activated relatively late as compared with an apposite endocardial point.[1, 5] Under such circumstances, a lead from an endocardial point reveals a deep QS deflection which is the reciprocal of an R wave recorded in a lead from an adjacent point on the epicardium.

(b) In bundle-branch block, excitation has been held to reach the endocardial aspect of the homolateral ventricle after spreading slowly across the septum from the normally activated contralateral ventricle. Thereafter spread over the endocardium occurs at the usual rapid rate, attended and succeeded by spread through the free wall of the ventricle in the ordinary fashion. As far as mechanically induced left bundle-branch block is concerned, the results reported in the present series of experiments afford no evidence incompatible with this concept of excitation.

It may be appropriate, however, to direct attention to an apparent inconsistency, the significance of which is questionable because it is derived from quantitative rather than qualitative considerations. In the normally activated heart, the QS deflection in left ventricular cavity leads consistently is of greater amplitude than the R wave recorded in leads from contiguous points on the ventricular surface. On the other hand, the S deflection which forms the final portion of complexes recorded in leads from the cavity of the left ventricle in left bundle-branch block commonly is of lesser amplitude than the final portion of the R wave recorded in leads from near-by points on the epicardium of the left ventricular wall. In attempting to account for this fact consideration may be given to the possibility that in certain portions of the septum, excitation may be spreading toward the cavity electrode late in the QRS interval at a time when excitation of the free wall is taking a course away from that electrode. The effects of these two processes would tend to neutralize each other at the cavity electrode but to complement each other at an epicardial electrode. Against this explanation is the improbability of appreciable portions of the septal myocardium being activated so late in the QRS interval.

An alternative explanation is that in bundle-branch block, excitation moves into the homolateral ventricle not only in the manner just described but also over more superficially disposed pathways from the contralateral ventricle. In such an event exploring electrodes within the cavity and on the surface of the homolateral ventricle would be subject to the combined effect of forces derived from endocardial-epicardial spread and of forces produced by a wavelike extension of excitation from the margins of the contralateral ventricle into the homolateral ventricle. At the epicardial electrode those forces would be of the same sign and would summate to give a large R deflection in the graphic record. At the cavity electrode, the relative negativity produced by endocardial-epicardial spread would be neutralized in part by the relative positivity induced by the wavelike extension from the contralateral ventricle. Hence the final S deflection in the cavity record would be of lesser magnitude than the R of the epicardial record.

Attention was directed to this latter possibility by results encountered in the course of experiments reported here. These results were obtained in experiments in which interventricular conduction disturbances were evoked by instillation of a traumatizing agent into a ventricular cavity. Although under these circumstances the complexes in leads from the surface of the ventricle were like those seen in bundle-branch block, the complexes in cavity leads consisted only of a broad R wave. At the same instant, distribution of potential within the electric field was such that a state of relative positivity existed at exploring electrodes on either side of the ventricular wall.

Such a distribution of potential might be encountered if endocardial-epicardial spread of excitation were replaced by a wavelike extension of excitation from the margins of the contralateral ventricle into the homolateral ventricle. Both epicardial and endocardial electrodes might then bear a similar spatial relationship to the spread of excitation through the intervening ventricular wall.

These proposals with respect to the spread of excitation in an uncomplicated bundle-branch block and in block complicated by subendocardial injury are made in a tentative fashion only. At no other point in this study is the need for further investigation so apparent a requirement before a solution of satisfying nature can be submitted.

3. *Arborization Block.* Under the term "arborization block" reference is made to the electrocardiographic phenomenon of QRS widening related to an intraventricular conduction disturbance other than bundle-branch block. That complexes of this type develop as a consequence of damage to a specialized conduction tissue localized to a region just beneath the endocardium has been rendered unlikely by the results obtained when traumatizing agents were placed in the ventricular cavities of isolated perfused hearts. However, complexes of strikingly similar form were recorded in experiments in which excitation moved down a strip of myocardium made up of fibers the axes of which were transverse to the long axis of the strip (fig. 11, complexes 13*a*, 15*a*, 9*a*). If such complexes develop clinically only when conditions are established simulating those of this strip experiment, the rarity of true arborization block becomes understandable.

Ventricular Strain Pattern. If the origins of the electrocardiographic changes associated with ventricular hypertrophy were established, even an attempt in passing to relate such changes and the results of these experiments would be unjustified. Since the best thinking on the problem contains much which is pure speculation,[6] the influence of data, however meager, may prove salutary. Attention may be directed to certain complexes in figures 3 and 7. The tracings in figure 3 were obtained in an experiment in which cocaine was introduced into the left ventricular cavity of an isolated perfused heart. As the complexes in a lead from the surface of the left ventricle evolved from a "normal" to a bundle-branch block configuration, complexes appeared in which the R wave was tall, the S-T segment slightly depressed, and the T wave inverted. These complexes look like those of the left ventricular strain pattern in precordial leads from regions overlying the left ventricle. In figure 7 are reproduced tracings obtained from a comparable experiment on the right ventricle, and here complexes of a right ventricular strain type appear.

The interesting sequences of complexes in these two experiments may represent no more than increasing degrees of interference with conduction through the left or the right bundle branch, affected little if at all by the concurrently developing changes in the subendocardial myocardium. Even if this is the case, these complexes reveal the many possible way stations on the course between normal conduction and complete bundle-branch block.

However interpreted, these results indicate that the origins of ventricular strain complexes could and may lie in disturbances in the spread of excitation secondary to functional or anatomic changes in subendocardially disposed tissues.

Conclusions

Direct-lead electrocardiograms have been recorded on isolated perfused dogs' hearts subjected to certain injuries designed to influence the spread of the excitatory process through the ventricular myocardium. These injuries were produced by the introduction into the left or right ventricular cavity of solutions or crystals of potassium chloride, silver nitrate, phenol or cocaine.

Injuries sufficiently severe to be attended by the electrocardiographic pictures of bundle-branch block did not evoke any specific effect which might be ascribed to arborization block consequent to destruction of Purkinje fibers. As complexes typical of bundle-branch block developed in epicardial leads, the QRS complex in leads from the ventricular cavity into which the traumatizing agent had been introduced

assumed an essentially monophasic character, with an R wave very similar to that recorded simultaneously from a contiguous epicardial lead. Apparently, endocardial and epicardial electrodes bore a similar spatial relationship to the spread of excitation through the intervening ventricular wall.

In an attempt to account for these findings, the hypothesis was proposed that the speed at which the excitatory process spreads through a certain segment of the myocardial syncytium depends upon the orientation of the fibers in that segment to each other and to the point of origin of excitation.

Testing of this hypothesis was undertaken by isolation of a segment of the ventricular wall, except for a limited attachment at one end of the strip. The spread of excitation down this segment was studied in relation to the disposition of the fibers constituting the strip. The presence of a band of fibers the long axis of which was parallel to the long axis of the strip appeared to be essential to rapid excitation of the segment. Whether these fibers were epicardial or endocardial made no difference.

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The Extremity and Circumferential Chest Lead Electrocardiogram in Induced Acute Coronary Insufficiency

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The extremity and circumferential chest lead electrocardiogram (twenty-two leads) was studied in 8 patients with generalized coronary insufficiency induced by exercise. Over the right chest, posteriorly and laterally, there was noted RS-T elevation similar to but less pronounced than that occurring in lead aV_R. These leads probably represent true or mixed cavity potentials. Standard leads revealed more marked RS-T alterations after exercise than did aV leads. In the left anterior chest leads, the greatest RS-T depression occurred in the left unipolar precordial leads representing the maximal voltage of the R wave—usually V_4 or V_5. The practical application of these findings is discussed in relation to routine two step exercise tests.

AN ELECTROPHYSICAL investigation of induced acute coronary insufficiency was undertaken by means of the twenty-two lead electrocardiogram, i.e., three standard, three augmented "unipolar" extremity, and sixteen chest leads completely circumscribing the thorax. We wished to study the RS-T segment alterations in these various leads in order to determine those showing maximal changes and those most representative of coronary insufficiency. We also desired to relate the findings in individual leads to the chamber and also to the area of the myocardium involved, i.e., subendocardial or subepicardial regions. We desired also to determine the comparative value of the different leads for possible application to the two step exercise test. Conventionally, the standard bipolar leads (I, II, III) and unipolar chest lead V_4 are routinely employed for this procedure. However, the increasing popularity of the augmented "unipolar" extremity leads (aV_R, aV_L, aV_F) and the six multiple unipolar precordial leads (V_1 through V_6) in clinical cardiology has prompted the question of any possible role of these newer leads in the interpretation of the exercise tolerance test.

Moreover, under certain circumstances, recording of leads taken circumferentially around the chest wall may be of value. In this study, we were anxious to determine whether or not there is any RS-T segment deviation in leads over the posterior and right side of the thoracic cage when there is RS-T segment depression after exercise in leads over the left anterior chest wall indicative of acute coronary insufficiency. We were particularly interested in a comparison of RS-T deviations in the right and posterior thoracic leads with those in lead aV_R.

Eight patients with established coronary artery disease with normal resting electrocardiograms were selected for this study. In each instance, a control resting electrocardiogram was taken. This consisted of the three standard limb leads, "unipolar" extremity lead (aV_R, aV_L and aV_F), and unipolar circumferential chest leads. The latter were taken as follows: the usual V_1 through V_6; V_7 (left posterior axillary line); V_8 (left midscapular line); V_9 (left paravertebral line); V_{9R} (right paravertebral line); V_{8R} (right midscapular line); V_{7R} (right posterior axillary line); V_{6R} (right midaxillary line); V_{5R} (right anterior axillary line); V_{4R} (right midclavicular line);* and lastly V_{3R} (midway between the conven-

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* V_7 through V_{4R} being at the horizontal level of the fifth anterior intercostal space.

TABLE 1.—*Extremity and Circumferential Chest Lead Electrocardiogram in Induced Acute Coronary Insufficiency*

	Case, Sex, Age															
	#1. S.I. M, 38		#2. E.T. F, 76		#3. M.L. M, 63		#4. I.M. M, 68		#5. B.M. M, 61		#6. N.G. F, 50		#7. D.B. F, 39		#8. M.L. F, 50	
	R	RS-T	R	RS-T	R	RS-T	R	RS-T	R	RS-T	R	RS-T	R	RS-T	R	RS-T
I	2	−1.0	3	−0.5	2	−0.75	4	−1.0	6	−1.0	3.5	−1.0	4	−1.0	5	−0.5
II	12	−2.0	11.5	−1.0	1	−1.5	5	−1.5	6	−1.25	7	−1.75	9	−2.0	12	−0.75
III	12	−1.25	7	−0.75	1	−1.0	3	−0.5	1.5	−0.5	4.5	−1.0	4.5	−0.5	7.5	0
aV_R	3	+1.5	0	+0.5	2	+1.0	2	+1.0	1	+1.0	0	+1.5	0	+1.5	0	+0.50
aV_L	1	0	1.5	+0.25	2.5	0	3	−0.3	3	−0.5	2	0	1.5	0	3	−0.25
aV_F	12	−1.5	4	−0.5	1	−1.0	5	−0.75	4	−0.75	5	−1.5	7	−1.5	9	−0.50
V_1	0	0	0	0	0	0	0	0	1.5	0	3	0	1	0	2	0
V_2	0	0	0.3	0	3	−0.25	1	−0.5	4	−0.5	7	−1.0	1.5	0	5	0
V_3	1.5	0	7	0	5	−1	4	−0.75	7	−0.75	10	−1.0	8	−1.75	8	0
V_4	2.5	−1.0	28	−3.5	7.5	−1.25	17	−1.5	16	−1.0	8	−1.75	16	−2.0	11	−1.0
V_5	9.5	−1.75	18.5	−2.5	7.5	−1.5	11	−1	18	−1.5	16	−2.0	13	−1.5	12	−1.0
V_6	9.0	−1.25	12.5	−1	4	−1	10.5	−1	8	−1.0	14	−1.0	10	−0.75	11	−0.75
V_7	7.5	−1.0	5	0	1	−0.5	8.5	−0.5	6	−0.75	9	−1.0	6	−0.5	9	−0.5

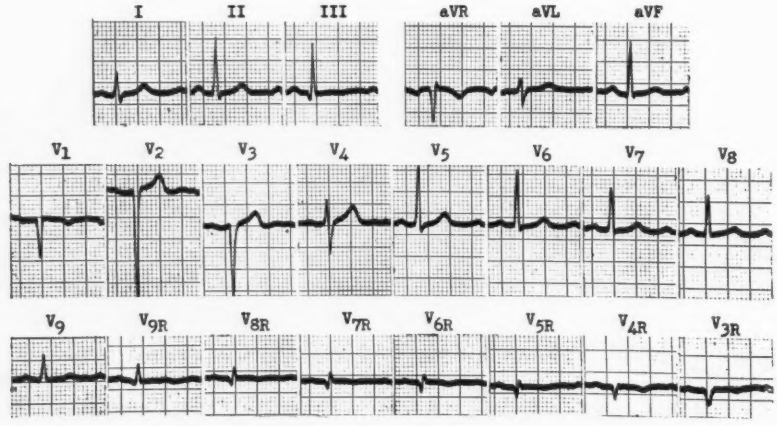

FIG. 1. S. I., male, age 38. Angina pectoris for 1 year. Control twenty-two lead electrocardiogram—normal.

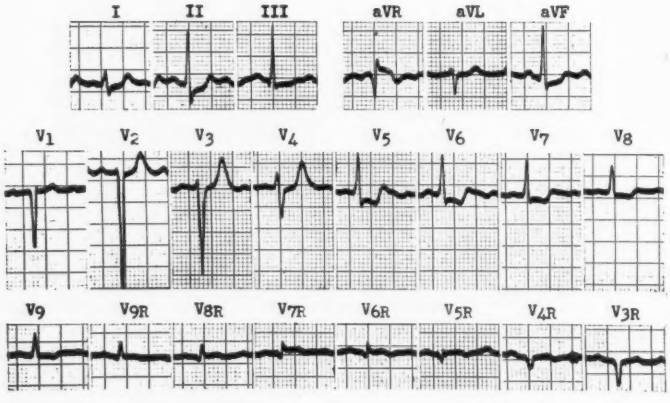

FIG. 2. S. I., male, age 38. Angina pectoris for 1 year. Twenty-two lead electrocardiogram after exercise discloses patterns of acute coronary insufficiency.

tional V_1 and V_{4R}). The Master two step exercise test[1] was then performed. After exercise the electrocardiogram was taken immediately and an endeavor was made to take all the aforementioned leads again within two minutes or less during the induced acute coronary insufficiency. To facilitate the recording of all these leads after cessation of the exercise, chest electrodes were left at their respective points and connected by separate wires to a specially constructed selector box which in turn was connected to the exploring electrode of a single channel direct-writing electrocardiographic machine equipped with an instomatic device (Sanborn).

In all 8 cases the exercise tolerance test was positive (see table 1). The electrocardiographic changes observed were similar to alterations occurring during spontaneous attacks of acute coronary insufficiency. The deepest depression of the RS-T segment in the chest leads occurred either in unipolar lead V_4 or V_5 (table 1) and in each individual case, the greatest depression occurred in the chest lead with the maximal voltage of the R wave. Leads taken on the right side of the chest showed only minimal elevation, usually exhibiting qR, QR, Qr or QS patterns. Lead aV_R in every case showed a significant elevation. These findings are illustrated by the following case. Figure 1 refers to a 38 year old male, S. I. (case 1, table 1), with a one year history of severe angina pectoris which led finally to cervicodorsal sympathectomy for attempted relief. The control resting twenty-two lead electrocardiogram is normal. Figure 2 demonstrates the patterns of acute coronary insufficiency in the twenty-two lead electrocardiogram after exercise. There is noted RS-T segment depression in leads I, II, III, aV_F and V_4 through V_8 and RS-T segment elevation in lead aV_R with minimal elevation in V_{6R} through V_{8R}. In all instances, the findings reverted to those of the control tracings within 10 minutes following cessation of exercise. In the cases studied, the electrocardiographic signs of acute coronary insufficiency were typically alterations of the RS-T segments with T wave abnormalities playing a relatively insignificant role.

Discussion

The electrocardiographic pattern obtained after exercise in patients with known coronary artery disease or myocardial injury, i.e., depression of the RS-T segment in routine "epicardial" leads, is due primarily to involvement of the cells in the subendocardial layers of the heart. In studies correlating electrocardiographic and anatomic findings in cases of acute coronary insufficiency Friedberg and Horn[2] and Master, Dack, Grishman, Field and Horn[3] have demonstrated that the RS-T depressions found in this condition are associated with subendocardial necrosis. Injury to the subendocardial surface of the left ventricle induced experimentally resulted in elevation of the RS-T segment in leads from within the cavity of the left ventricle, while epicardial leads taken at the same time directly over the damaged subendocardial areas have shown RS-T segment depression.[4, 5, 6] Wener, Scherlis, Sandberg, Master and Grishman,[7] in using esophageal leads, have shown that in patients with angina pectoris the depression recorded in standard and precordial leads immediately after exercise was regularly associated with elevation of the RS-T in the esophageal leads taken simultaneously at atrial levels reflecting left ventricular cavity potentials. Most pronounced depression of the RS-T segment was at times recorded in the lower esophageal electrocardiogram which reflected the posterior surfaces of the left ventricle.

Kisch[8, 9] has shown that if the right side of the heart is acutely damaged epicardially, the R-T segment is highly elevated in the right chest lead and is deeply depressed in the left chest lead. If the left side of the heart is acutely damaged epicardially, the opposite occurs in the chest leads, i.e., the R-T segment is elevated in the left chest lead and depressed in the right chest lead. In our series of cases, depression of the RS-T segment occurred over the left chest, therefore, we would expect elevation over the opposite side of the chest. The pattern usually obtained over the right side posteriorly was a qR, QR, Qr, or QS which probably represents either a true cavity or mixed cavity potential. The elevations seen

in leads from the right chest posteriorly and laterally are minimal because of the small voltage recorded at this distance from the heart and because vector relationships to the horizontal level selected may not be optimal to record maximal RS-T deviations. In our series of cases, lead aV_R appeared similar to true or mixed cavity potentials and is probably similar to esophageal leads at the atrial level. In all instances, the RS-T elevations in aV_R were much more pronounced than those observed over the right posterior and lateral chest leads.

The greatest RS-T depression was recorded in unipolar precordial leads over the left anterior chest reflecting the maximal voltage of the left ventricle, i.e., the unipolar precordial leads with the tallest and widest R wave, which is usually V_4 or V_5 depending upon the position of the heart within the thorax. The RS-T depressions seen maximally at V_4, V_5 or V_6 are similar to depressions seen in lower esophageal leads representing potentials from the posterior aspect of the left ventricle. In this study unipolar chest (V) leads were employed in preference to bipolar chest leads (CR, CL, or CF).

Although circumferential chest leads after exercise may furnish additional data concerning the electrophysical phenomena associated with acute coronary insufficiency, our studies indicate that a single unipolar precordial lead is adequate for routine diagnostic purposes. It must be emphasized that in taking one unipolar precordial lead during an exercise tolerance test, the position of the electrode must be over that area of the chest with a maximal voltage of the R wave, despite the presence or absence of an S wave, in order to obtain the maximal depression of the RS-T segment. Therefore, routinely all six precordial leads should be taken at rest, i.e., in the control, to determine the optimal placement of the precordial electrode in order not to miss localized induced coronary insufficiency.

Theoretically, in acute coronary insufficiency, RS-T segment alterations in extremity leads will be more marked in the customary bipolar standard leads I and II than in unipolar extremity leads (aV_R, aV_L and aV_F) since the former will represent the RS-T depression in lead V_L or V_F minus any RS-T elevation in lead V_R. This fact was substantiated in the cases studied (see table 1). Therefore the standard extremity leads are preferable to the aV leads in performing exercise tests for coronary insufficiency, despite the augmentation of potentials in the latter leads and regardless of the electrical axis of the heart.

It must be emphasized that the cases described above all showed generalized coronary insufficiency on effort because of underlying severe coronary artery disease. Hence, RS-T alterations were noted in many of the twenty-two leads selected for study with greatest deviations occurring most frequently in lead V_4 or V_5 and lead II, in that order.

Conclusion

1. Eight patients with angina pectoris due to coronary artery disease were studied. The electrocardiogram during a spontaneous episode of angina pectoris and also after exercise disclosed a classic picture of coronary insufficiency, i.e., RS-T alterations and T-wave inversions in the customary twelve leads (leads I, II, III, aV_R, aV_L, aV_F, and V_1 through V_6).

2. In the same patients the two step exericise electrocardiogram was repeated with the chest electrode placed around the chest (V_1 through V_9 and V_{9R} through V_{3R}) and twenty-two leads were taken. RS-T depressions were found on the left side anteriorly and posteriorly. Over the right chest posteriorly and laterally there were qR, QR, Qr or QS patterns with elevation of the RS-T segment after exercise. Lead aV_R in the cases of induced coronary insufficiency studied shows RS-T elevation in higher voltage than in unipolar chest leads taken posteriorly and to the right.

3. These findings corroborate the fact that if RS-T depressions are obtained over one area of the heart, then, according to the laws of electrophysics, RS-T elevations must be present elsewhere. The elevation over the right posterior and lateral aspect of the chest probably represent true or mixed cavity potentials.

4. The greatest RS-T depression is found in

unipolar precordial leads over the left anterior chest reflecting the maximal voltage of the R wave which is usually V_4 or V_5 depending on the position of the heart. Therefore, in selecting the position of the precordial electrode for the two step test, the lead recording the greatest voltage of the R wave should be chosen. Lead II is the best standard lead to employ.

5. The standard bipolar extremity leads show more marked RS-T deviation than the augmented "unipolar" extremity leads and are therefore preferable for the exercise tolerance test.

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Characteristics of the Unipolar Precordial Electrocardiogram in Normal Infants

By ROBERT F. ZIEGLER, M.D.

The electrocardiogram should have as much clinical value in infants and children as in adults. Such value, as in adults, must depend upon an accurate knowledge of normal standards which change progressively during infancy and early childhood. Some of the more important measurements in the precordial leads of normal infants are presented and discussed. These measurements, the amplitude and the time of inscription of the intrinsic deflection, are believed to indicate the changing relationship between the mass of the right and left ventricles, and on the basis of these data it is also believed that an earlier and more accurate diagnosis of ventricular hypertrophy can be made at any age.

RECENT interest in the various forms of congenital and acquired heart disease in infants and children, coupled with a complete lack of adequate standards for the normal electrocardiogram in these age groups, has made apparent the need for the sort of study which will provide useful knowledge about this important method of examination. Heretofore little interest has been given the subject of electrocardiography in children. In fact, even the current literature is unfortunately replete with statements of the limitations and lack of value of this type of data in evaluating the cardiac status of infants and children. It seems probable that this attitude results from a lack of knowledge rather than a specific limitation in the value of the method and should consequently be dispelled by adequate investigation. A detailed study of the electrocardiograms of 650 normal infants and children has already been made and is being published separately.[1] It has been suggested that in addition to the original material a brief summary of the most important characteristics of the precordial electrocardiogram in infants and young children might be of supplementary value. It is therefore the purpose of this communication to present an abstract of this material which will include data pertaining to the form and measurements of the ventricular deflections in unipolar precordial leads of infants and children from birth to the age of three years (table 1). It is assumed, probably correctly, that the extremity leads of the electrocardiogram are of less value than those from the precordium. These will consequently not be discussed in the present paper.

The two most important practical aspects of the precordial electrocardiogram in normal infants are (1) the form of the QRS complexes in leads from the right and left sides of the precordium, particularly as this pertains to the detection of an abnormal degree of right or left ventricular hypertrophy in this age group, and (2) the direction and configuration of the T waves in each of the precordial leads, as they pertain to the detection and evaluation of various types of cardiac abnormalities.

TABLE 1.—*Distribution of Cases According to Age.*

Age	Number of cases
Birth–24 hours	20
1–7 days	26
7–30 days	25
1–3 months	15
3–6 months	14
6–12 months	18
1–3 years	27
Total	145

With regard to the first of these two problems, it has formerly been considered that in the extremity leads right axis deviation constitutes evidence of right ventricular enlargement, and more or less parallels anatomic measurements of relative right ventricular mass

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in normal infants. The limitations of this electrocardiographic criterion have been discussed elsewhere and need not be repeated here. Supposedly more accurate criteria, derived from measurements in the precordial lead electrocardiogram, have also been discussed in the original publication[1] and may be applied to an analysis of the electrocardiograms of normal infants and children. Among these are the following important measurements:

1. The amplitude of the R wave in the precordial leads expressed as a percentage of the amplitude of the RS deflection in the same lead.

2. The time of onset of the RS deflection in the precordial leads, measured from the beginning of QRS in simultaneous standard lead I.

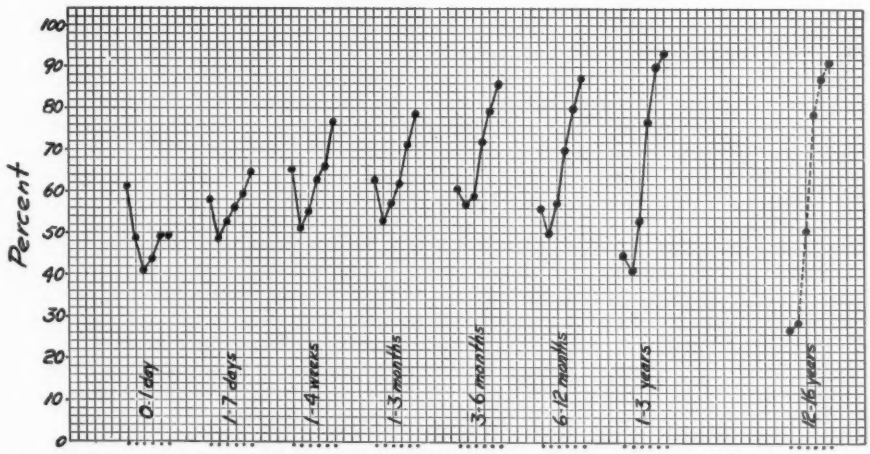

FIG. 1. The amplitude of intrinsic deflection in unipolar precordial leads expressed as a percentage of RS in the same lead. Each group of six points represents measurements for each of the precordial leads V_1 through V_6. Note the progressive changes during the period of early infancy and the comparison with the adult pattern attained at the age of about 12 to 16 years. (All figures are reproduced by the courtesy of Charles C Thomas.[1])

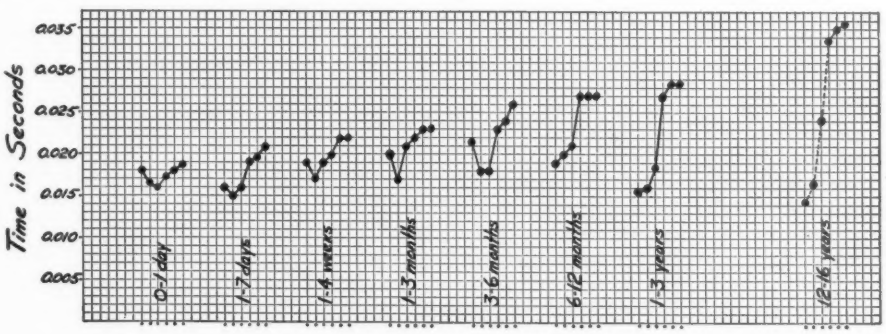

FIG. 2. The time of onset of the intrinsic deflection in precordial leads measured from the beginning of QRS in simultaneous standard lead I. Each group of six points represents measurements for each of the precordial leads V_1 through V_6. Note the progression of changes during early infancy and the relation to the adult pattern reached between age groups of 12 to 16 years.

As observed in figures 1 and 2, well marked changes in these measurements are apparent with age. If, as seems reasonable, they represent some relation between the size of the two

ventricles, then it may be concluded that there is evidence that the right ventricle is normally larger in comparison with the left from birth to the age of 1 to 3 years than in older children and adults. It may also be seen that the two sets of measurements parallel each other rather closely. Various electrocardiographic studies have utilized similar measurements as criteria for right or left ventricular hypertrophy, but no such criteria have as yet been available for the rapidly changing phases of infancy and early childhood. It would appear evident on the basis of such data as summarized here and published in more complete detail in the reference cited[1] that abnormal degrees of right or left ventricular enlargement should be detectable with reasonable accuracy at any age and probably even with early degrees of enlargement. As will be shown in subsequent publications, these electrocardiographic criteria have actually made it possible to detect the presence of single chamber enlargement during infancy and childhood with greater accuracy than conventional roentgenographic methods and at a time when the latter may reveal completely normal findings.

TABLE 2.—*The Per Cent Incidence of Various T-Wave Patterns from Birth to the Age of 3 Years*

		V1	V2	V3	V4	V5	V6
0–24 hours	+	74.1	74.1	40.0	59.3	46.6	55.7
	−	7.41	3.7	40.0	22.2	13.4	14.8
	0	0	3.7	0	7.41	0	3.7
	+−	18.5	18.5	20.0	11.1	40.0	25.9
1 day–1 wk.	+	18.75	18.75	27.3	56.2	100.0	87.5
	−	62.5	62.5	36.4	25	0	0
	0	0	6.25	0	6.25	0	6.25
	+−	18.75	12.5	36.4	12.5	0	6.25
1 wk.–1 mo.	+	0	25	31.3	100	100.0	100
	−	83.5	33	25.0	0	0	0
	0	0	0	6.25	0	0	0
	+−	16.5	42	37.5	0	0	0
1–3 mos.	+	11.5	19.2	12.5	80.8	100.0	100
	−	77.0	61.6	12.5	7.7	0	0
	0	3.8	0	0	0	0	0
	+−	7.7	19.2	75.0	11.5	0	0
3–6 mos.	+	0	21.5	12.5	100	100.0	100
	−	100	64.5	12.5	0	0	0
	0	0	0	0	0	0	0
	+−	0	14	75.0	0	0	0
6 mos.–1 yr.	+	0	0	0	73	100	100
	−	100	91	57	4.3	0	0
	0	0	0	0	0	0	0
	+−	0	9	43	22.7	0	0
1–3 yrs.	+	0	4.3	15.4	92	100	100
	−	96	77.5	38.4	4	0	0
	0	0	0	0	0	0	0
	+−	4	18.2	46.2	4	0	0

The second problem is that concerned with the description of the direction and configuration of the T waves in the precordial leads. An interpretation of these observations is not within the scope of the present study. It might first be stated that current concepts of the precordial T wave pattern in normal infants and children have been somewhat in error because of such technical difficulties as the failure to isolate carefully each exploring point over the precordium and the use of bipolar instead of unipolar precordial leads. Great care was exercised in the present study to insure the technical accuracy of each record. The most interesting feature of the precordial T wave pattern in normal infants is the sequence of changes which occur independently of any comparable changes in QRS during the first three or four days of postnatal life. During the first 24 hours after birth the T waves are usually upright in lead V_1 and inverted in leads V_5 and V_6. During the next 48 to 72 hours there follows a progressive inversion of the T waves in leads V_1 and V_2 and elevation of those in leads V_5 and V_6. While the physiology underlying these phenomena remains unknown for the present, the practical clinical implications are apparent. In particular, the same type of change has been observed in somewhat exaggerated form and with a longer duration in infants born to diabetic mothers and in infants with congenital defects which impose a primary increased work load on the left side of the heart. The characteristic T-wave pattern in the precordial leads of older infants and young children consists of slight to moderate elevation of the S-T segment with multiphasic or inverted T waves in leads from the right and mid precordium and upright T waves in leads from the left side of the precordium. The direction and configuration of the precordial T waves in these age groups are indicated in table 2.

It seems apparent that the accurate differentiation of the normal and abnormal heart in

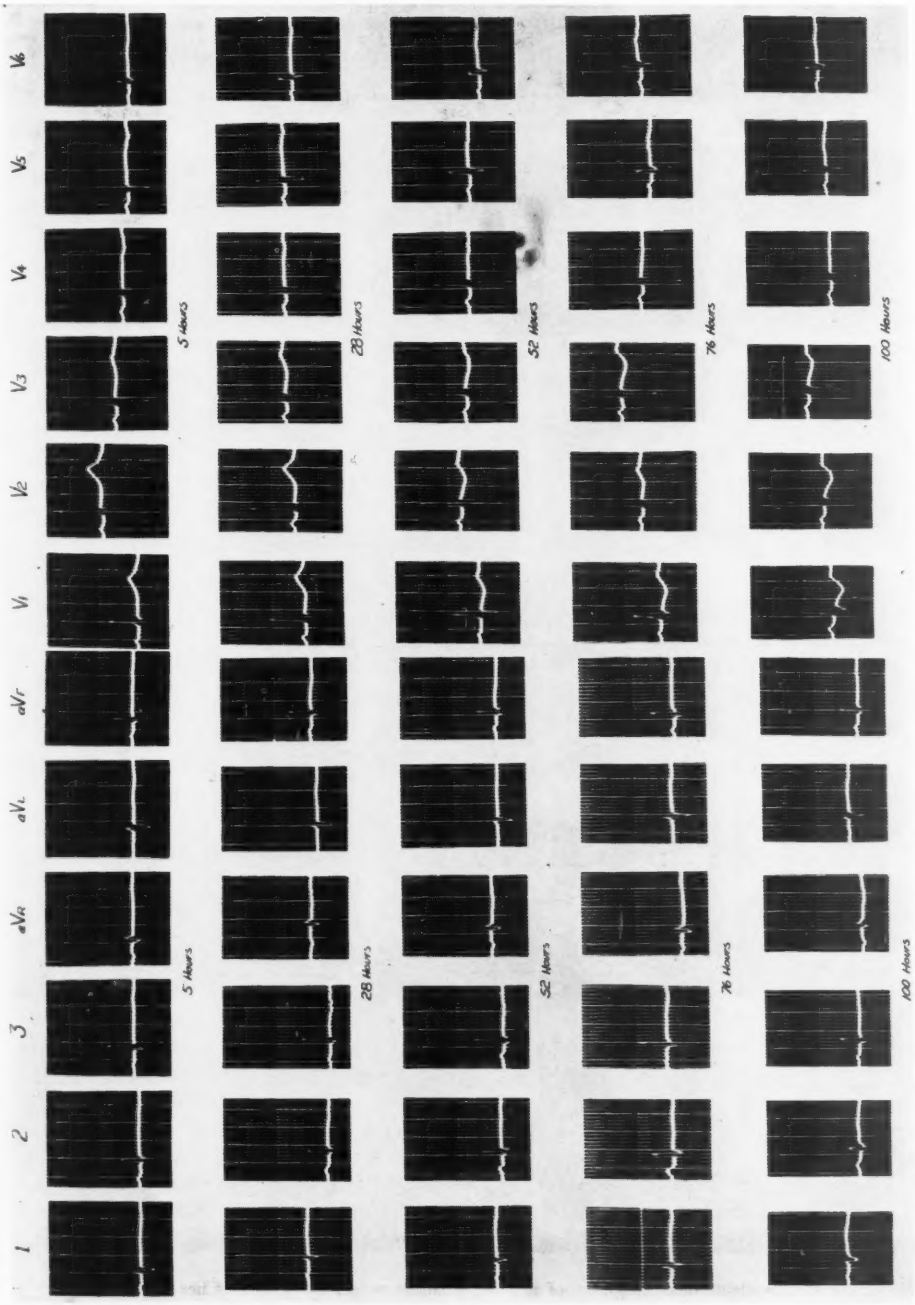

FIG. 3. Representative electrocardiographic patterns in a normal infant during the first four days of life. In the precordial leads note the progression of the T waves from positive to negative in leads from the right side of the precordium and the reverse pattern in leads from the left side of the precordium. For comparison see figure 4.

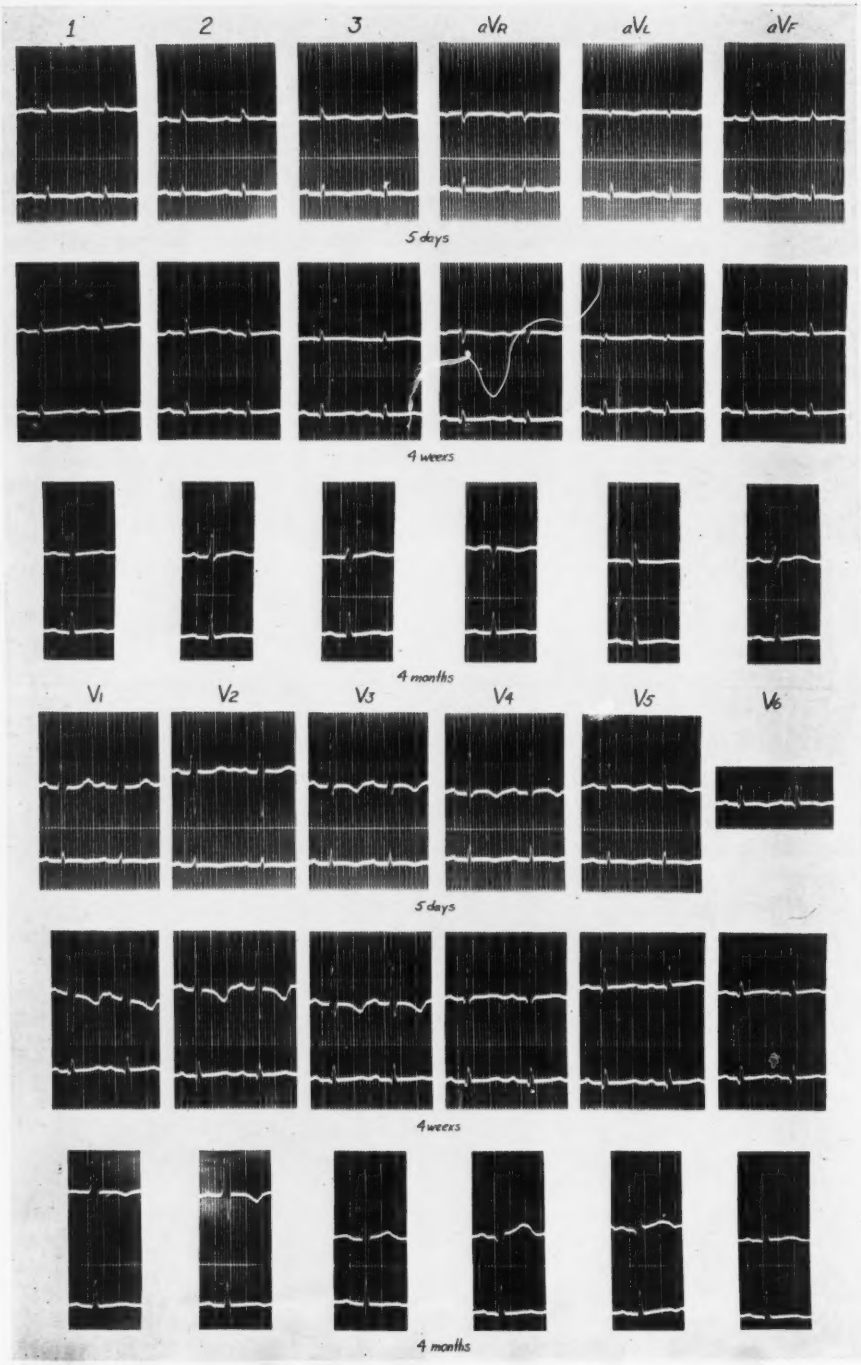

FIG. 4. The electrocardiogram of a baby without other evidence of heart disease born to a diabetic mother. The upper tracing in each figure is as labeled; the lower one is simultaneously recorded standard lead I. Note the sequence of T wave changes comparable to those seen in early infancy in normal babies.

infancy and early childhood as well as the exact diagnosis of cardiac defects in this age group depends upon the recognition and proper evaluation of just such ventricular patterns as those described. Two sets of electrocardiograms demonstrating the characteristic patterns of a normal infant and a baby without later evidence of heart disease born to a diabetic mother are shown in figures 3 and 4.

The clinical implications of these electrocardiographic findings in normal infants and children deserve further comment. It has already been emphasized that one of the most important practical applications of these data is the accurate and early detection of single chamber enlargement as well as the recognition of other specifically abnormal ventricular patterns. An important corollary of the improved diagnostic accuracy resulting from this knowledge of the electrocardiograms includes, in addition to a better ability to establish a differential clinical diagnosis, greater knowledge about the natural history of congenital cardiac defects together with an improved perspective of problems relating to their prognosis and treatment. As an example, the exact knowledge that a certain degree of left rather than right ventricular hypertrophy is present in an infant with a noncyanotic congenital malformation of the heart may help confirm the clinical diagnosis of patent ductus arteriosus long before other so-called "typical" findings become manifest. This in turn will have at least two advantages. It will, in the first place, make possible definitive therapy if necessary and by so doing may frequently save a life which might otherwise be lost. It will also provide information necessary to a more complete understanding of the basic problems involved in the natural history of this defect. These would include such problems as the relationship between the size of the ductus and the degree of left ventricular hypertrophy, the relationship between compensating or complicating pulmonary hypertension and the size of the right ventricle, the significance of increasing heart size and others. Similar importance of the electrocardiogram could be discussed for all the various forms of congenital cardiovascular defects.

A number of other important applications of this study of the electrocardiograms of normal as well as abnormal infants and children which constitute the subject for further investigation and report may be listed to include the following: (1) The evaluation of so-called borderline electrocardiographic patterns, such as those involving intraventricular conduction defects. (2) Detailed investigation of the form and significance of the initial ventricular deflections. (3) The recognition and the evaluation of so-called physiologic and other degrees of right bundle branch block. (4) The determination of the significance of intraventricular conduction defects in the development of electrocardiographic patterns of ventricular hypertrophy. (5) The evaluation of the significance of unstable electrocardiographic patterns.

These all constitute the subjects for other papers being prepared for publication

Summary

The principal characteristics of the ventricular deflections in the unipolar precordial electrocardiogram of normal infants from birth to the age of 3 years are described briefly. More complete details have been published elsewhere.[1] These characteristic features include: (1) evidence of a normal degree of relative right ventricular prepondrance, consisting of large amplitude and late onset of the intrinsic deflection in leads from the right side of the precordium; (2) the presence of upright T waves in leads from the right side and inverted T waves in leads from the left side of the precordium during the first 24 hours of life, followed by a gradual progression to inverted T waves in leads from the right side and upright T waves in leads from the left side of the precordium during the subsequent two to four days; and (3) the presence of multiphasic or inverted T waves in leads from the right and mid precordium in older infants and young children. The practical clinical significance of these various precordial ventricular patterns is emphasized.

REFERENCE

[1] Ziegler, R. F.: Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill., Charles C Thomas. In Press.

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Emotion and the Circulation

By MARK D. ALTSCHULE, M.D.

ACCEPTANCE of the Platonic doctrine that all bodily ills proceed from the spirit led medical authors of antiquity, the Middle Ages and the Renaissance to ascribe cardiac diseases to emotional disorders almost exclusively. Postmortem studies, impressively collected by various authors, notably Zimmerman,[1] appeared to confirm this general idea and to support such concepts as "dying of a broken heart," where cardiac rupture was found in grief, or "hardness of heart," in which pericarditis was found in individuals notorious for cruelty. In the early nineteenth century, Corvisart and his followers, Burns, Testa and Kreysing, likewise believed emotion to be the most important cause of heart disease. The cause of cardiac and aortic dilatations was confidently stated to be the driving inward of the bodily humors during psychic stress. Sudden development of dropsy, cardiac hypertrophy and aortic aneurysms immediately following a single severe emotional upset was often described. Corvisart and Testa stated that heart disease increased markedly during and after the French Revolution and attributed this phenomenon to the disorder of the times. Bertin, a decade later, held that seeming increases in cardiac disease were due only to its being recognized more certainly. This controversy of over a century ago sounds familiar in the present. In spite of increase of knowledge of pathologic anatomy in the nineteenth century, etiologies of cardiovascular diseases remained obscure. The tendency to ascribe conditions of unknown etiology to emotional disturbances persisted, as exemplified by one authority of the 1870's, who stated with assurance "It is not surprising that in the present day, when the worry of life and strain on the feelings in all ways are so vastly intensified, that there should be strong evidence to show the increase of cardiac affections"; Balfour expressed similar ideas 25 years later and today some cardiovascular diseases still are considered to be due to psychic disorder.

The problem that plagues the cardiologist arises from the fact that he sees evidence daily of the influence of emotion on the circulation but has at hand no extensive body of physiologic data that might illuminate his clinical observations. For the most part, the psychosomatic studies of the circulation merely emphasize what the competent internist appreciates, namely, that emotion may cause cardiovascular symptoms. The present discussion will analyze available physiologic studies and will attempt to relate them to clinical phenomena. Reference will be made only to the heart and peripheral blood vessels; consideration of renal and gastrointestinal circulation will be omitted.

PERIPHERAL VASCULAR SYSTEM

Physicians of antiquity believed that specific emotions caused specific changes in the pulse; this belief has persisted, in various forms, during the past 25 centuries. For instance, early in the present century, Wundt, in his *Gefuhlstheorie*, classified feelings rigidly in three pairs, i.e., pleasure-pain, tension-relaxation, and excitation-calm, and his followers claimed to have

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observed specific changes in the pulse wave corresponding with each. This work, reviewed by Leshke[2] in 1914, formed a seemingly convincing body of evidence which now is regarded as invalid. Recent work on specificity in peripheral vascular reactions to emotion[3] evokes doubt because of skepticism regarding the authors' ability to characterize exactly the feelings experienced by their subjects during short experiments and because of the absence of suitable control periods.

Many physiologic studies of general effects of psychic factors on peripheral circulation are available.[4] Cutaneous vasoconstriction in the hands and feet during emotion has been amply demonstrated; this change manifests itself by cooling of the parts and, because of stasis, excessive deoxygenation of the capillary blood. In ordinary circumstances, changes in the hands are due both to arteriolar and venular constriction, whereas those in the forearm are largely venular in origin; on the arterial side only the terminal cutaneous arteries, and not the radial, metacarpal and digital arteries, usually are involved. In extremely severe emotion, however, spasm of the radial artery may be detected. As a consequence of spasm of arterioles and venules, changes in cutaneous capillaries occur; these are visible on microscopic examination of the vessels of the fingernail folds. All the changes described are minimized by vasodilating agents such as alcohol, carbon dioxide or warmth.

The immediate vasoconstriction of emotion is effected via the sympathetic nervous system and a sympathectomized extremity does not show it. The hypothalamus contains centers governing generalized vasoconstriction and vasodilatation but the occurrence in emotional states of vasomotor changes limited commonly to the acral areas raises the possibility that the impulses arise in the cortex. On the other hand, it is possible that vasomotor changes in general are most marked in the acral regions so that weak discharges from the hypothalamic centers cause changes which are detectable only in the extremities. At any rate, the importance of cortical impulses in vasomotor phenomena is now recognized; this will be discussed below, in relation to hypertension.

Although most studies of peripheral flow emphasize unpleasant emotions in causing the changes observed, there are data which show that strong pleasurable emotions may give rise to identical peripheral vascular phenomena.[5] The thesis that subjects who show marked vasomotor changes with pleasurable emotions are expressing subconscious guilt consequent to experiencing such feelings is not supported by psychologic studies. In addition, as Lombard showed a century ago, and others have corroborated since,[6] vasoconstriction in the extremities occurs also during concentration not obviously emotionally colored.

Peripheral vasomotor phenomena of emotion do not parallel regularly the facial expression of emotion and even less so the verbal description of it. Whether conscious or unconscious feelings are the more important is unknown; however, emotional vasoconstriction disappears during sleep, when, according to psychoanalytic thinking, unconscious emotions are at their height.

Patients with persistent and marked emotional vasoconstriction exhibit coldness of the extremities and are intolerant to cold temperatures. Confusion may arise with the symptoms of hypothyroidism or anemia so that patients may needlessly receive thyroid or antianemic medications.

The vasoconstrictor effects of emotion may aggravate manifestations of such peripheral vascular diseases as arteriosclerosis, thromboangiitis obliterans, post-traumatic causalgia and Raynaud's disease. In addition, men with a previous history of excessive vasomotor reaction to emotion are markedly susceptible to frost-bite and trench foot.[7, 8] Rheumatoid arthritis of the hands and feet is also demonstrably influenced by emotions and excessive vasoconstriction in this disease actually has been demonstrated.[9]

Fragmentary observations[10] suggest that subjects with unstable peripheral vascular systems develop conditioned reflexes involving this system more easily than do others; this may suggest a possible mechanism whereby the peripheral vascular system becomes the one which expresses emotion in some individuals. In addition, emotionally unstable individuals exhibit excessive acral vasoconstriction as a

consequence of concentration itself,[6] which suggests that vasomotor as well as cerebral emotional mechanisms may be abnormal.

Physiologic phenomena underlying blushing and blanching of the face and neck have not been studied; here is a promising field for observation on specificity of emotional responses, for blanching with fear and blushing with embarrassment are well known. On the other hand, various feelings may cause either pallor or flushing in different individuals or in the same individuals at different times. The belief that easy blushing is evidence of a marked paranoid personality has no support in extensive observation, and is a conclusion based on an a priori interpretation of the symptom. Vasodilatation consequent to fever, external heat, imbibing of alcohol, or emotional upset is known to be followed by urticaria in some individuals.[11] Acetylcholine is released locally during vasodilatation and it is well known that acetylcholine is a whealing agent. Whether it acts as such, or through the liberation of histamine, is not established, however. Development of hives under these circumstances in some individuals and not in others is not understood.

Cardiac Rate

Marked changes in heart rate occur in relation to emotion. Poor correlation between changes in pulse rate and the facial or verbal expression of emotion is regularly found.[12] Variation in rate from minute to minute may be marked.[12] As a rule the rate is accelerated in emotional reactions but at times it may be abnormally slow. In some instances the sinus bradycardia is part of a syncopal reaction, while in others the bradycardia is not the precursor of any such reaction. The cause of the rapid and marked variation in rate is not known, although at times it may be due to sinus arrhythmia correlated with hyperventilation.

Changes in pulse rate during strong emotion are of the same magnitude in normal and in neurotic subjects. Neurotic subjects, however, experience more severe emotional reactions than normal subjects during mild stresses. The neurotic may, moreover, be more aware of emotional tachycardia than the non-neurotic subject. The pulse rate in exercise in neurotic subjects will be discussed below, in relation to neurocirculatory asthenia.

The relation of emotional tachycardia to conscious appreciation of emotions has not been defined. Emotional tachycardia subsides during sleep, a fact used in differentiating anxiety from thyrotoxicosis. On the other hand, during sleep a noise, insufficient to awaken the sleeper or make him exhibit overt evidence of startle, may increase the pulse rate by a third.[12] This phenomenon appears to vary with the depth of unconsciousness.

It is generally presumed that tachycardia of emotion is related to sympathetic hyperactivity, or production of excess epinephrine. However, norepinephrine, which does not increase pulse rate but merely raises the blood pressure, is probably liberated from the adrenal medulla together with epinephrine. An additional complication arises from the fact that acetylcholine in small amount causes tachycardia and in larger amount slows the pulse. It is known also that the brain contains areas which cause tachycardia when stimulated. It is evident that the precise cause of emotional tachycardia is not known.

Rapid heart rates in neurosis may lead to mistaken diagnoses of heart disease or thyrotoxicosis; neurotic patients who complain of tachycardia may be given antithyroid drugs or digitalis and may become disabled owing to bad advice regarding activity. It should be noted that palpitation in neurosis need not signify occurrence of a rapid heart rate; palpitation may be experienced with normal or slow heart rates if sudden rises in blood pressure occur, if the rhythm is irregular, or, on occasion, with no change in the circulatory mechanisms.

Cardiac Rhythm

Routine examination of neurotic subjects may not reveal the occurrence of any arrhythmia other than sinus arrhythmia, but every cardiologist has seen occasional instances in which auricular flutter, fibrillation or tachycardia, frequent auricular, nodal or ventricular premature beats, the Wolff-Parkinson-White syndrome, or minor degrees of heart block

appear recurrently in emotionally unstable individuals without heart disease. At times the arrhythmia apparently develops in relation to some unusual emotional stress, but on other occasions similar stresses do not cause it; conversely, the arrhythmia may appear in the absence of overt emotional upset. The same fact holds in patients with established diagnoses of organic heart disease; partial heart block may increase in degree, or premature beats may become more numerous during emotional upset. The arrhythmias seen in relation to emotion are usually those produced by hyperactivity of the vagus nerve, i.e., arrhythmias involving the S-A node, the auricles and the A-V node; in the case of ventricular premature beats the effect of circulating epinephrine, or of sympathetic stimulation must be considered.

Electrocardiogram

Papers claiming that abnormalities of QRS complex or of T waves indicative of altered myocardial function occur in neuroses or are produced in normal subjects by emotion are unconvincing; changes shown appear to be due to variations in cardiac rate and in position of the heart. Examination made here of several hundred electrocardiograms in instances of emotional disorder corroborates the findings of others who showed no deviation from the normal.

Cardiac Output and Work: Circulation Time

That measurement of cardiac output in tense or frightened subjects yields values that are high relative to the basal has long been known to physiologists. The earlier work of Grollman[13] and the more recent studies of Stead and co-workers[14] and Hickam and associates,[15] all employing accurate methods, showed that emotion may increase cardiac output by two-thirds, and occasionally more; the cardiac output may vary markedly from minute to minute. These observations showed no relation between type of emotion and change in cardiac output. Hickam and co-workers[15] and Wolff and Wolff,[16] using the ballistocardiograph, found greater increases in cardiac output in many patients during emotional stresses; the latter authors claimed that some types of emotion caused decreases in the output of the heart. The ballistocardiograph is not accurate when the pulse rate changes markedly and rapidly. Discrepancies between the work of Wolff and Wolff[16] and that of other authors may be due to the method used; however, the observations of Hickam and associates,[15] who used the same method, do not support the concept of relation between type of emotion and circulatory change. Rises in cardiac output owing to emotion are greater than increases in oxygen consumption which occur at the same time; the cardiovascular changes resemble those which follow injection of small amounts of epinephrine.[15] Cardiac work is proportionately increased.

Circulation time is usually accelerated in emotional tension although marked emotionally-induced venoconstriction in the forearm may cause some slowing in the observed time and so give no true indication of the increase in cardiac output.

Change in cardiac output during anxiety in patients with heart disease but without failure are similar to those in normal subjects[15, 17]; in congestive failure, however, little or no increase in cardiac output (and work) occurs during anxiety although the pulse rate rises. The increase in metabolism induced by emotion in these circumstances results in further deoxygenation of capillary blood and exacerbation of the anoxia already present.

Stevenson and his co-workers[17] studied the effects of exercise on cardiac output in anxiety and found the rise to reach higher absolute values and also in some instances to be greater in amount than when the subjects exercised while relaxed. Makinson[18] found the increase to be normal but more prolonged in neurosis. However, the use of a method of low accuracy makes acceptance of these data only tentative. Nevertheless a metabolic effect of emotion, i.e., failure to oxidize carbohydrate completely, as described below, suggests that the cost of work is higher during stress and therefore the circulatory response in exercise should be greater than in normal circumstances.

Increases in resting cardiac output by about

half owing to anxiety is not significant in causing emotional dyspnea during exertion except when the effort attempted is maximal; the maximal possible cardiac output is not approached during moderate physical activity and the patient does not need the cardiac reserve lost as a result of the increase in resting cardiac output occasioned by emotion. In patients with serious organic heart disease but no failure, the increases in cardiac output during strong emotion, may, if long continued, act in a manner like that of thyrotoxicosis, anemia, fever and other conditions which strain the heart and precipitate decompensation.

Cardiac Discomfort: Sudden Death

A variety of sensations seemingly localized about the heart occur during emotional reactions. The clutching discomfort occasioned by fear is well known; it differs from angina pectoris, according to those who have experienced both. The heavy sensation associated with sadness is also commonly experienced. The mechanism of these sensations is completely unknown.

Another type of discomfort, commonly seen in neurosis and more particularly in neurocirculatory asthenia, is the typical persistent, sticking pain close to the left breast. Its occurrence does not depend on changes in cardiac rate or rhythm, although in occasional patients it occurs only with premature beats or with palpitation. The mechanism of its production and the pathways of its transmission are not known. Commonly it is associated with persistent tenderness over the left chest although each of the two symptoms may occur without the other. Anxiety pain is occasionally confused with angina pectoris, leading to induction of a needless state of invalidism in the patient; this occurrence is a reflection on the physician who makes the error, for anxiety pain and anginal pain have only the most superficial resemblance. The confusion between anxiety pain and angina pectoris vitiates all of Dunbar's work[19] on the latter disorder.

Attacks of true angina pectoris may be precipitated by "disturbance of the mind," in the words of Herberden. In the presence of coronary arterial insufficiency, increases in cardiac work owing to emotion may cause anginal pain or may cause exertion more readily to induce it. John Hunter, whose clinical history and postmortem findings contributed to the modern theory of angina pectoris, often stated, "My life is at the mercy of any scoundrel who chooses to put me in a passion." Hunter's death occurred during a dispute with the Governors of St. George's Hospital regarding the exclusion of students whom he considered to be victims of a prejudice against the Scotch. The pain of angina pectoris occurs when the work of the heart is increased to a degree which cannot be paralleled by increased flow through diseased coronary arteries; the importance ascribed by Wolff and Wolff[16] to their findings of a lowered cardiac output in one patient during one attack of angina induced by emotion may be criticized in view of the fragmentary data, obtained by a method of low accuracy.

Another possible mechanism for the precipitation of anginal pain during emotional stress has not been studied adequately. That cooling of the skin of the hands favors the occurrence of anginal attacks in patients with the syndrome has been established[20, 21]; the fact that strong emotion usually causes cooling of the skin over the acral areas may therefore be significant.

Discussion of mechanisms for producing anginal attacks applies also to myocardial infarction. Sudden death during emotional strain has been recognized for at least 25 centuries as a common occurrence in the middle-aged or elderly. Although ventricular fibrillation may account for some, in many such instances myocardial infarction is the cause for this accident; it must not be concluded, however, that strong emotion is the sole or the most important cause of myocardial infarction. That strong pleasurable emotions may be as dangerous in causing sudden death as grief, rage or despair is important in relation to advising patients regarding their daily activities. Benjamin Rush described how "... the door-keeper of Congress, an aged man, died suddenly, immediately after hearing

of the capture of Lord Cornwallis's army. His death was universally ascribed to a violent emotion of political joy. This species of joy appears to be one of the strongest emotions that can agitate the human mind."

Syncope

A fundamental phenomenon in syncope is strong vagal discharge causing marked sinus bradycardia; occasionally minor degrees of heart block and ventricular escape may occur. Total peripheral resistance decreases markedly and blood pressure falls[22]; there is also evidence of generalized loss of venous tone and, to judge from the cutaneous vasoconstriction which develops,[23] of pooling of blood in the viscera. The cutaneous vasoconstriction, manifested by disappearance of visible capillaries in the fingernail fold and by smallness of the superficial veins of the arm, may result from a sympathetic discharge elicited by the falling blood pressure. Cardiac output measured with the patient recumbent is normal,[22] but in the upright position it is markedly decreased.[23] In animals stimulation of areas in the frontal lobes causes hypotension and bradycardia; the relation of these findings to emotional syncope may be important.

Tendencies to recurrent fainting in neurotic patients may be ameliorated by the drugs effective against increased vagal tone, i.e., atropine, ephedrine and the like.

Hypertension

Much has been written on the importance of emotion in hypertension and opinions vary. Most cardiologists believe that psychic influences are among those which most strongly influence the course of the disease; on the other hand, some internists and most psychiatrists feel that emotional factors actually cause essential hypertension. The first of these opinions is well established but the second is not securely founded in observation. The present discussion will not attempt to resolve this issue but only to point out certain factors that must be borne in mind in considering it. Hypertension may cause only mild symptoms and accordingly introverted patients are most aware of these minor complaints; high incidence of neurosis in patients with complaints of hypertension therefore results. Also, since emotional upset does aggravate hypertension, the incidence of neurosis is high in patients with early or moderate hypertension. In addition, stresses of various types cause more marked and more persistent increases in blood pressure in neurotic than in normal subjects. Definition of physiologic mechanisms responsible for exacerbation of hypertension is difficult in the present state of knowledge, a fact that has not deterred many authors from doing so. There are observations which show that anxiety in normal or neurotic subjects is accompanied by decreased peripheral resistance; the diastolic blood pressure is elevated only occasionally and remains unchanged or falls for the most part. The systolic pressure rises parallel with increases in cardiac output.[14-17] These changes resemble effects of injection of small amounts of epinephrine. However, there is good evidence that shows that in essential hypertension the peripheral resistance is increased, both systolic and diastolic pressures rising, while the cardiac output remains normal. It is evident that the cardiovascular physiology of essential hypertension differs from that of anxiety. Nevertheless it is true that anxiety further elevates systolic pressure in hypertensive subjects and increases cardiac work greatly. The fact that norepinephrine is also liberated during stimulation of the adrenal medulla is also important. It acts entirely on peripheral blood vessels, increasing peripheral resistance and not influencing cardiac output directly, thereby producing changes resembling those of essential hypertension. To assume that one adrenal medullary hormone alone, epinephrine, is liberated during stress in normotensive subjects while the other, norepinephrine, is liberated alone in hypertensive subjects is not reasonable; however, work should be done to ascertain whether stress of short duration results largely in epinephrine effects, while stress of long duration causes predominately norepinephrine effects, as work of Bulbring and Burns[24] suggests may be possible.

The cold-pressor test in normotensive patients with anxiety causes rises in blood

pressure which at most are only slightly greater than normal[25] and are much smaller than those found in hypertensive patients or some of their normotensive siblings. This finding again suggests that anxiety is not fundamental to essential hypertension.

Another humoral mechanism has been invoked to explain how anxiety may cause lasting hypertension. Decrease in renal blood flow, consequent to renal vasoconstriction, may occur in emotional stress; it has been suggested that renal ischemia so induced may give rise to elaboration of renin, and so cause elevation of both systolic and diastolic pressures without increasing cardiac output. Against this hypothesis is the fact that renin is not found in the blood in essential hypertension. In addition, not all patients with essential hypertension exhibit the changes in renal vascular dynamics required by this concept.

Excellent work in animals and more recently in man[26] has extended knowledge bearing on nervous pathways which carry vasoconstrictor impulses from the brain. Existence of vasoconstrictor centers in the hypothalamus has long been known; recently it has been shown that stimulation of the frontal cortex, especially that of its posterior orbital surface, elevates blood pressure. The location of this area in the general region in which is situated cortical representation of visceral changes and of somatic movements associated with expression of emotion is highly significant.

Some patients with essential hypertension exhibit significant changes in blood pressure in relation to variations in the intake of salt. The fact that a tendency toward salt retention may possibly exist during emotional stress, as discussed below, makes it necessary to consider this mechanism as possibly involved in relations between emotion and hypertension in some patients.

In spite of uncertainties regarding the manner in which emotion exacerbates hypertension, clinical observations nevertheless puts the relationship between the two on a sound basis; observation thus far, however, lends no support to the concept that emotion causes essential hypertension. Statements that certain types of personality or emotional conflict are the cause of the disorder are ill-founded and should be received with skepticism.

Neurocirculatory Asthenia

The importance of neurocirculatory asthenia has been rediscovered during every war in the course of the last century; there is no evidence that it is increasing in frequency. Its relation to neurosis is indicated not only by the nature of its symptoms, but also by the fact that the physiologic changes induced by exercise in patients with various types of neurosis are similar to those considered characteristic of neurocirculatory asthenia. A physiologic difference between these two groups of patients lies in the fact that on the average changes are greater in neurocirculatory asthenia; however, there is much overlapping of the two groups.[27]

In addition to pain and precordial tenderness discussed above, symptoms pertinent to the present discussion consist in diminution in tolerance to exercise owing to abnormally severe palpitation, dyspnea, or fatigue.

In emotionally disturbed subjects, exercise causes a greater rise in pulse rate than in the same subject when not upset, or in normal subjects; the pulse rate falls slowly after the exercise. The mechanism underlying this phenomenon is not known; the concept held in some quarters that hyperventilation is the cause of the tachycardia is not securely founded. The severity of the palpitation, due both to the markedly abnormal pulse rate and also to the patients' increased awareness of symptoms, results in disinclination toward exercise. If tachycardia is very marked during exercise in a neurotic subject it is possible that some impairment of circulatory function might develop owing to lessened filling of the heart due to shortening of diastole. Otherwise tachycardia is important only because of discomfort it may cause.

To consider neurocirculatory asthenia solely as a state in which the flesh is willing but the spirit weak is an error, for when patients with neurocirculatory asthenia, or indeed with

neurosis, exercise, evidence of a metabolic disorder becomes evident[27, 28]; minor degrees of this disorder may be apparent at rest also. The resting blood lactate level may be slightly elevated in some, but during exercise it rises regularly to a higher level and remains elevated longer than in normal subjects doing the same work. Oxygen consumption during strenuous work is not increased as much as in normal subjects and consequently there is a large and prolonged oxygen debt. Associated with excessive and prolonged rises in blood lactate in exercise there are corresponding increases in respiration, so that the carbon dioxide content of expired air falls and carbon dioxide may be washed out of the blood; during work the respiratory rate and minute volume increase more than in normal subjects and remain elevated for an abnormally long period after the end of exertion.

Mechanisms responsible for this metabolic phenomenon are not established but the changes observed are consistent with the effects of adrenocortical hormones known to be liberated during stress. Vital capacity and venous pressure at rest and after exercise are normal, and so no possibility of significant cardiac or pulmonary insufficiency need be considered. The exertional dyspnea of emotion is based upon impairment of lactic acid metabolism and the fact that neurotic patients are discomforted more than normal subjects by visceral symptoms. These mechanisms, important in neurosis or emotional upset in normal subjects, are all the more so in congestive failure.

Emotional dyspnea, since it does not involve stasis in the lungs or the venous system, is not associated with orthopnea, a fact useful in differential diagnosis. Patients with neurocirculatory asthenia may do large amounts of hard labor under some circumstances and need not show the excessive prostration exhibited by patients with congestive failure who attempt exertion beyond their capacities; as a rule, however, emotional dyspnea causes enough disability to force the patient into some limitation of activity. Nevertheless there is no harm in the patient's exceeding what he believes to be his capacity for exercise. Misdiagnosing the condition as myocardial insufficiency may do harm to a nervous patient if marked revision of way of life is advised.

Some Metabolic Effects of Emotion

Metabolic disturbances found in emotional disorders are numerous and complex; many are not pertinent to the present discussion and only three will be considered.

An extensive literature, based on work in animals, has shown that discomfort or emotional stress stimulates the hypothalamic center that regulates the function of the hypophysis and results in liberation of antidiuretic hormone. This effect is shortlived in normal animals but excretion or inactivation of this hormone is slowed in the presence of liver damage, such as exists in congestive failure. That some edematous cardiac patients retain more water than salt is recognized, and this finding suggests the importance of antidiuretic hormonal effects as a mechanism of edema formation in heart disease. Patients with congestive failure regularly exhibit retardation of water diuresis as do patients with mental disturbances also.[29] Patients with mental disorders also show abnormally small responses to the injection of diuretic drugs.[29] The above discussion regarding one possible relation between emotion and exacerbation of edema in heart disease is largely theoretic and is designed only to call attention to the problem.

Patients with emotional disorders show many evidences of increased activity of pituitary-adrenocortical mechanisms. It has been shown also that distressing thoughts are followed by physiologic evidence in normal subjects, of increased formation of adrenocortical hormones. That these hormones favor salt retention is well known and accordingly this phenomenon must be taken into account in consideration of those patients in whom diuresis with the commonly successful measures is unsuccessful.

One action of the adrenocortical hormones liberated during stress is to impair carbohydrate metabolism so as to retard removal of

lactate from the blood. This mechanism is basic in neurocirculatory asthenia, as discussed above, but also must be of importance, when present in congestive failure, in contributing to dyspnea, since the lactate metabolism is already markedly impaired in myocardial insufficiency.

Comment

Physiologic effects of emotion on the circulation in health and disease are many and varied. Their importance lies in the facts that (1) they may exacerbate cardiovascular diseases; (2) their manifestations may resemble those of coronary sclerosis or myocardial insufficiency and so lead to erroneous diagnosis, and (3) their occurrence may call attention to the presence of emotional disorders not previously recognized.

No comment has been made relative to the effect of disease itself in causing emotional upset which in turn acts unfavorably upon the initial condition; this is true when the condition is organic heart disease or cardiovascular neurosis. An example is afforded by Sir Walter Scott who stated, "what a detestable feeling this fluttering of the heart is . . . I know it is nothing organic, and that it is entirely nervous but the sickening effects of it are dispiriting to a degree." This problem involves one of the most important aspects of the relation between patient and physician.

The problems raised by emotional disorders are probably not more numerous now than they were in the past, although they are probably different in character. Psychiatric and other medical writings of the past, from those of Burton down to those of the present, recurrently exclaim at the rapid spread of emotional disorders consequent to loosening of family ties, disintegration of morals, loss of influence of the Church and deterioration of economic security. It is startling to find that Erb, for instance, used these same explanations at the turn of the century, a period which today is nostalgically considered to have been one of stability and contentment. It is difficult to accept the pronouncements of today's Cassandras regarding trends in the incidence of emotional disorders. The importance of neurosis may seem particularly large today as a consequence of the fact that measures are developed in rapid succession for the exact diagnosis and specific treatment of many diseases; no such measures exist in the field of emotional disturbances and so, by comparison, they cause the physician more perplexity and dissatisfaction than any other group of disorders.

Except for the fact that the cardiovascular changes in startle reactions are similar in nature if not degree in various individuals, no consistency is encountered in the occurrence or character of cardiovascular phenomena which may appear in relation to environmental factors which influence the psyche. The emotional significance of the environmental factor to the individual patient determines the occurrence and in a measure the severity of the response to it. On the other hand, except in a small minority of instances where the nature of the cardiovascular response to emotional stress is evidently determined by neurotic identifications or by conditioning in the past, there is no indication as to the mechanisms which result in the appearance of each of the various types of cardiovascular change.

In spite of the lack of a body of definitive data explaining the mechanisms underlying the occurrence of emotional reactions, the reasons for their variations in degree and nature, and the manner in which they cause bodily changes, there is no lack of positive statements bearing on all of these matters in the current literature. Much of the current writing on mechanisms whereby emotional situations cause cardiovascular symptoms consists in validation by anecdote, and is no more conclusive in establishing etiology than the writings of half a century ago that regularly ascribed heart attacks to the eating of spoiled or exotic foods. Attempts to prove that specific diseases are associated with or the consequence of specific types of personality arouse skepticism because of their lack of control studies, the limited amount of data presented, or evidence in some cases that the author is ignorant of the criteria used in recognition of the disease in question. Concepts which relate specific illnesses to specific types

of emotional conflicts likewise are not convincing in that they appear to be based on superficial resemblances of one or a few of the many characteristics of the clinical syndrome to one or a few of the many characteristics of the conflict; it is not established, moreover, that conflicts are single, simple and invariable, or that they can become known or understood completely. Symbolic explanations currently encountered in the psychosomatic literature also invite skepticism. Acceptance of symbolic formulations regarding cardiac symptoms require acceptance of one of two hypotheses: (1) that the heart is a thinking organ, a concept established in the minds of the ancients but not seriously considered in recent times since Vireý stated more than a century ago that the heart originates thoughts and sends them to the brain via the vagi, or, (2) that specific changes in cardiovascular function in emotion always are willfully selected (consciously or unconsciously) by the patient, a concept that has no basis in substantial evidence. Similarly, attempts to explain symptoms as the result of vagotonic or sympathicotonic trends in patients on the basis of reactions of the circulation to epinephrine, atropine, pilocarpine and to various maneuvers involving autonomic reflexes, are not grounded in acceptable theory and are vitiated by inadequate observation and circular reasoning.

John Hunter wrote "There is not a natural action in the body, whether voluntary or involuntary, that may not be influenced by the peculiar state of the mind at the time." It may be taken for granted that the course of any illness can be influenced by emotional factors, and accordingly the physician must seek evidence of their presence in every case. The lack of adequate data for systematizing information regarding reactions of patients to emotional factors makes it essential for physicians to understand in general what these factors might be and to learn as much as possible about the life and personality of each patient in particular. Evaluation of the significance of emotional factors and their treatment will test his every art, for there is no skill that can be learned quickly and precisely in these matters. Although the barbiturates and other drugs are helpful at intervals, they are less so, and at times may be harmful, in the long run. Circulatory disorders consequent to severe neurosis cannot, as a rule, be alleviated to any great degree or for any length of time without psychiatric treatment. On the other hand, the milder emotional disturbances aroused in normal subjects by ordinary vicissitudes of everyday life, and the somewhat more serious ones precipitated by serious cardiac illness, can be handled satisfactorily, if recognized, by the artful physician.

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ABSTRACTS

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BLOOD COAGULATION

Kay, J. H., Hutton, S. B., Jr., Weiss, G. N., and Ochsner, A.: Studies on an Antithrombin. III. A Plasma Antithrombin Test for the Prediction of Intravascular Clotting. Surgery **28:** 24 (July), 1950.

Antithrombin levels and prothrombin times were determined daily after a major surgical operation in 120 unselected cases. Fifty-three patients had antithrombin levels of 1:16 or less at some time during the postoperative period; of these, 23 had prothrombin times shorter than 20 seconds. In the latter group, 13 developed clinical evidence of thrombosis or embolism. None of the remaining 67 patients, whose antithrombin levels were above 1:16, presented evidence of thrombosis or embolism. In another series of cases, alpha tocopherol and calcium gluconate were administered, the results suggesting that the antithrombin level could be raised in this manner. It was therefore concluded that the routine postoperative use of these medications might be of value in eliminating intravascular clotting.

ABRAMSON

Shapse, J. B., and Wright, L. T.: Effect of Aureomycin on the Clotting Time of the Blood. Angiology **1:** 306 (Aug.), 1950.

Aureomycin was administered by oral or intravenous route to 30 patients; the dose was usually 500 mg. twice daily. Lee-White clotting times were determined before the drug was given and at 6, 12, 24, and 48 hours after the initial dose. The variations in blood coagulability were not of sufficient magnitude to be of clinical significance.

WESSLER

de Takats, G.: A Sensitized Clotting Time. Angiology **1:** 317 (Aug.), 1950.

A heparin-sensitized clotting time is described and its use in evaluating the coagulability of the blood in normal and disease states is presented in a small group of patients. The author believes that the test is simple, reliable, and sensitive. Shortened clotting times were observed only in patients with acute thromboembolic phenomena. Prolonged clotting times were observed following operations, trauma, hemorrhage, and anticoagulant therapy. The heparin-sensitized clotting time parallels prothrombin values. It is suggested that the test may be used as a guide in anticoagulant therapy.

WESSLER

Smith, R. W., Margulis, R. R., Brennan, M. J., and Monto, R. W.: The Influence of ACTH and Cortisone on Certain Factors of Blood Coagulation. Science **112:** 295 (Sept.), 1950.

The authors determined the effect of cortisone and ACTH on clotting times, platelet count, undiluted and plasma-diluted prothrombin time, heparin level, circulating eosinophil count, and plasma accelerator (Ac) globulin, and antifibrinolysin. In normal controls a single 20 mg. intramuscular injection of ACTH produced a significant increase in circulating heparin (or heparinlike substance) with a parallel prolongation of the clotting time.

Although considerable variation existed from patient to patient under continued ACTH administration, there was an initial transient increase in protamine titers and clotting times; a slight but significant lowering of clotting time during therapy, which returned to control levels when the hormone was withdrawn; a varying increase in the level of circulating heparin material, which continued after ACTH withdrawal; and significant changes in both the per cent prothrombin and in the diluted-plasma prothrombin times, which are inverse to the change in protamine titers. Variations were also noticed in the levels of plasma Ac-globulin and two-stage prothrombin and antifibrinolysin. The significance of these changes to blood coagulation in patients receiving ACTH or cortisone is not apparent, but the release of heparin may be related to the hyperheparinemia of anaphylactic shock.

WAIFE

CONGENITAL ANOMALIES

Prader, A., and Rossi, E.: Investigation of the Cellular Blood Constituents in Morbus Caeruleus (Congenital Cyanosis). II. Iron and Hemoglobin Metabolism. Helvet. paed. acta **5**: 159 (May), 1950.

In a large group of children with morbus caeruleus, the authors found a mean increase in the total hemoglobin of 163 per cent (26.6 per Kg. of body weight), in the serum iron of 123 per cent (201 y per cent) and in the serum bilirubin of 198 per cent (1.49 mg. per cent). The direct van den Bergh reaction was always negative. Indirect evidence indicates that total body iron, intrinsic and extrinsic iron metabolism, and iron requirement are raised. There is a rise in the total hemoglobin metabolism, but in proportion to the total hemoglobin, the metabolism is normal (based on the reticulocyte count and the rate of urobilin excretion). The main cause of the raised iron and bilirubin is the increased hemoglobin metabolism. The reduction of the plasma volume and the hypoxic liver damage may play a supporting role. There is no accelerated hemolysis. Cases with normal or low serum iron are masked iron deficiency anemias. They are characterized by a low color index and a decreased mean corpuscular volume. A review of literature indicates that the observed changes in the iron and hemoglobin metabolism are probably present in each true polyglobulia (polyglobulia of altitude, polycythemia vera).

AUTHORS

Prader, A., and Rossi, E.: Investigation of the Cellular Blood Constituents in Morbus Caeruleus (Congenital Cyanosis). III. Erythrocytosis. Helvet. paediat. acta **5**: 172 (May), 1950.

The authors studied 50 children with morbus caeruleus. The hemoglobin, number of erythrocytes, and hematocrit value are considerably increased, the color index is normal. Mean corpuscular volume and mean corpuscular diameter are increased (macrocytosis), mean corpuscular thickness is normal, and spherical index is rather decreased (platycytosis). There is an anisocytosis, but no poikilocytosis. The mean corpuscular hemoglobin is normal; the mean corpuscular hemoglobin concentration is rather decreased. Maximum osmotic resistance is increased; minimum resistance is decreased.

The polyglobulia often masks an iron deficiency anemia. In these cases the erythrocytes have most of the signs of an iron-deficient anemia, and the usual increase of the amount of iron in the serum is absent. Nearly the same erythrocytic syndrome as in the blue disease is encountered in other polyglobulias due to lack of oxygen and in liver diseases. Lack of oxygen is possibly the direct or indirect (hypoxic liver damage) cause of the changes of the erythrocytes. It may be an adaptation mechanism for a better utilization of oxygen.

AUTHORS

Prader, A., and Hollander, L.: Investigation of the Cellular Blood Constituents in Morbus Caeruleus (Congenital Cyanosis). IV. Leukocytes and White Blood Cells. Helvet. paediat. acta **5**: (May), 1950.

The authors studied the number of white blood cells and the differential count in 41 cases of morbus caeruleus. They found a slight leukopenia with a slight decrease in the absolute number of eosinophils, monopenia, and lymphopenia. Lack of oxygen may be the direct cause, and a hyperfunction of the adrenal cortex (stage of resistance of Selye's general adaptation syndrome) the indirect cause.

AUTHORS

Monad, O.W.F., Katch, E. H., and Vandooren, M. F.: Considerable Improvement following Exploratory Thoracotomy in Two Cases of Tetralogy of Fallot. J. Thoracic Surg. **20**: 158 (July), 1950.

Two cases of tetralogy of Fallot are reported in which surgical anastomosis between the systemic and pulmonary vascular systems could not be accomplished for technical reasons. Great improvement followed the thoracotomies with extensive dissections of pleural adhesions, the mediastinum and pulmonary hilum. The possible explanations for the improvement were (1) the creation by surgical trauma of new vascular adhesions in the pleura and mediastinum which might function as little "ducti arteriosi"; (2) a sympathetic vasomotor effect on the pulmonary circulation as a result of prolonged dissection in the region of the subclavian artery.

KLOSK

Jokl, E., and Mackintosh, R. H.: Sudden Death of Young Athlete from Rupture of Ascending Aorta. Lancet **2**: 54 (July), 1950.

The authors report the sudden death of a 15 year old athlete following wrestling and weight lifting, with detailed autopsy findings. Multiple congenital anomalies were found, of which stenosis of the isthmus of the aorta was the most important. The obstruction produced dilatation of the aorta above the isthmus, overdevelopment of the internal mammary arteries, and hypertrophy of the left ventricle. Also present were persistant thymus with active Hassall's corpuscles, hypoplastic thin-walled arteries, and a general abundance of lymphatic tissue. The immediate cause of death was rupture of the ascending aorta.

TANDOWSKY

Marquis, R. M.: Ventricular Septal Defect in Early Childhood. Brit. Heart J. **12:** 265 (July), 1950.

Four instances of ventricular septal defect are reported, 2 with necropsy confirmation, characterized by (1) underdevelopment, (2) absence of cyanosis, (3) liability to respiratory infection, (4) tendency to heart failure in early childhood, (5) Roger's murmur, (6) accentuation of the pulmonic second sound, (7) occasional diastolic murmurs down the left sternal margin, (8) clinical, radiologic and electrocardiographic evidence of enlargement of both ventricles, and (9) radiologic evidence of enlargement of the pulmonary artery and hilar vessels. This anomaly may be associated with tricuspid insufficiency, aortic insufficiency, absence of aortic septum, partial subaortic stenosis, hypoplastic aorta, and absent membranous septum. The prognosis of this group is poor.

SOLOFF

Rossi, E., Grob, M., and Gutewa, J.: Capillaroscopy before and following Surgery in Congenital Heart Disease. Helvet. paediat. acta **5:** 279 (June), 1950.

The authors describe and illustrate with microphotographs capillary changes observed in the nail fold of 51 children with various types of congenital heart disease. The most pronounced abnormalities were found in cyanotic cases (tetralogy of Fallot) and consisted of enlargement, widening, and tortuosity of the capillary loop, especially in its venous limb. In cases with less marked cyanosis (Eisenmenger complex and truncus arteriosus communis) the changes were similar but of lesser degree. In interventricular and interatrial septal defects, an almost normal capillary pattern was present. In cases of coarctation of the aorta, the capillary picture resembled that usually associated with arterial, hypertension, e.g., elongated capillary loops with a narrowed afferent limb.

In cases of tetralogy of Fallot as well as of coarctation, a definite improvement of the condition of the capillaries could be observed within three weeks following successful surgery. Thus, capillaroscopy can be used to assess relatively early the benefit of an operation in congenital heart disease.

PICK

Donzelot, E., Durand, M., and Metianu, C.: Notes on Congenital Heart Block and Presentation of Two Cases. Acta cardiol. **5:** 319, 1950.

Congenital heart block is rare, only about 100 cases being described in the literature. Of these about 30 are beyond dispute, 7 being accompanied by autopsy reports. Embryologic studies have shown that the bundle of His develops earlier than the ventricular seputm. Therefore, a ventricular septal defect cannot explain the dissociation by interruption of the bundle.

Two instances of complete A-V dissociation were observed in the authors' series of 650 cases of malformations of the heart. One was found at the age of 4 months, the other at the age of 7 years. The diagnosis of malformation of the heart was tentative in both patients. In the first, with an auricular rate of 127 per minute and ventricular rate of 62, there was a complete situs viscerum inversus accompanied by a complex malformation; in the second, whose auricles contracted at a rate of 88 and ventricles at a rate of 50 per minute, an Eisenmenger complex was diagnosed. Both cases fulfilled Yater's and Mahaim's criteria for the diagnosis of a congenital heart block.

BRUMLIK

Segers, M.: Left-Sided Origin of the Right Subclavian Artery. Acta cardiol. **5:** 182, 1950.

The author describes 3 cases in which the right subclavian artery originated on the left side. In each case the vessel crossed the esophagus in its abnormal course from left to right and produced an unusual indentation of this structure (visualized after the ingestion of barium). In 2 cases the esophagus was found to be compressed in its posterior aspect and in 1 case in its anterior aspect. Dysphagia was present in 1 case.

PICK

Lequime, J., Denolin, H., Goksel, F., Jonnart, L., and Wybauw, M.: Interauricular Communication. Clinical and Physiopathological Study of Four Cases. Acta cardiol. **5:** 302, 1950.

In 4 patients in whom a clinical diagnosis of interauricular communication was established, catheterization of the heart and hemodynamic studies were performed. The volume of blood passing through the pulmonary artery was far higher (7.34 to 19.32 liters per minute) than the aortic output (2.59 to 6.66 liters per minute). This difference was due to an arteriovenous auricular shunt (4.75 to 13.15 liters per minute); a venoarterial shunt of insignificant amount was probable in 2 cases. With exercise, the coefficient of oxygen utilization (ratio of oxygen used to pulmonary ventilation) increased consider-

ably in contrast to pulmonary stenosis, which showed a decrease of this coefficient under the same conditions of the test. The pulmonary function appeared normal.

BRUMLIK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Behrmann, J. H., Hipp, H. R., and Heyer, H. E.: Pain Patterns in Acute Myocardial Infarction. Am. J. Med. **9:** 156 (Aug.), 1950.

Behrmann and his co-workers discuss the prognostic value of the duration, location, radiation, and mode of onset of pain in 150 patients with proven acute myocardial infarctions. Patients with the longest duration of pain had the highest mortality rate. Patients in whom the pains were confined to the thorax without radiation had higher mortality than those in whom the pain radiated to the extremities and neck. The mode of onset of pain in acute myocardial infarction is variable. It may be painless; it may consist of a few, short pains of intermittent type which are not severe; it may appear suddenly without premonitory pain; it may appear following premonitory pain of long duration; or it may appear after a long period of angina.

HARRIS

Akert, K.: Insulin Myocardosis. Schweiz. med. Wchnschr. **80:** 1010 (Sept.), 1950.

A 39 year old schizophrenic patient with normal cardiovascular findings died suddenly three hours following injection of 140 units of normal insulin, on the one hundred sixteenth day of his third series of therapeutic insulin shocks. At postmortem examination, extensive areas of old and recent myocardial necrosis (sarcolysis) were found in the heart. The coronary arteries were intact but at histologic examination showed marked contraction of the internal muscular layer. The liver showed lobular necrosis, and multiple gastroduodenal ulcers were present in the gastrointestinal tract. Changes in the endocrine organs were marked and consisted of eosinophile conglomerates in the anterior pituitary lobe, diffuse hyperplasia of the adrenal cortex and a relative increase of the alpha cells of the islets of the pancreas.

The author attributes the abnormal findings in the various organs to exhaustion of endocrine adaptation to the repeated and massive insulin treatment. The immediate cause of death was probably spasm of the coronary arteries.

PICK

Mainzer, F.: Heart Contusion in Coronary Disease. Cardiologia **16:** 287, 1950.

The author observed 2 patients with coronary disease, evidenced electrocardiographically by right bundle branch block, who, following a slight injury distant from the heart, developed transient signs of contusion (concussion) of the heart. In the first case acute dilatation of the heart was accompanied by a transitory inversion of the T wave in leads III and aV_F. In the other, acute left heart failure and pulmonary edema succeeded the accident, accompanied by a fall in blood pressure and inversion of the T wave in lead V_2. Statistical data, experiments reported in the literature, and clinical observations suggest that in elderly people cardiac contusion may be a pathologic reaction of a diseased heart to a moderate, otherwise harmless injury.

PICK

ELECTROCARDIOGRAPHY

Segers, M.: The Relationship between the Electrocardiographic Pattern of Intraventricular Block and That of Infarction. Compt. rend Soc. de biol. **144:** 592 (April), 1950.

The author injected a 1 per cent solution of strychnine into a circumscribed area of the left ventricle of the rabbit. He observed in a precordial lead the development of an intraventricular conduction defect (late intrinsicoid deflection) which changed at times to the pattern of myocardial infarction, characterized by a normal QRS duration, a typical high take off of the T wave, but without appearance of a Q wave.

Basing his conclusions on previous experiments, the author ascribes both patterns to a block developing at the junction between the Purkinje system and ordinary myocardium. While the pattern of intraventricular block represents a mere delay of activation of the injected area, the pattern of infarction would indicate complete exclusion of this region from the wave of excitation (mute zone). Similar patterns, representing incomplete and complete "Purkinje-myocardial block" can also be seen in clinical electrocardiography.

PICK

Reindell, H., Klepzig, H., Weyland, R., and Berg, W.: Correlation of Extremity and Thorax Electrocardiograms in Metabolic Disturbances and Damage of the Heart. Ztschr. f. Kreislaufforsch. **39:** 226 (April), 1950.

The authors report a correlation of the incidence of ST-T alterations in standard and multiple chest leads in cases with myocarditis or following injection of adrenalin or digipuratum in normal cases. Only in 1 per cent of the observations did they note ST-T anomalies in the chest leads which were not present in the standard leads. On the other hand, the precordial electrocardiogram was normal in 16 per cent of cases with a definitely abnormal extremity electrocardiogram. The authors question the value of precordial leads for the recognition of infectious or toxic damage of the myocardium.

PICK

Morin, G., Jouve, A., Albouy, M., and Velasque, P.: Experimental Verification of the Interpretation of Electrocardiograms Obtained with Precordial Chest Leads. Compt. rend. Soc. de biol. **144:** 554 (April), 1950.

The authors registered in dogs a series of precordial leads at different levels of the thorax. Frozen sections made exactly through these various levels permitted an exact correlation of various electrocardiographic patterns with the size and anatomic position of that part of the ventricles nearest the exploring electrode.

The authors were unable to establish a relationship between the variations of potentials at various precordial points and the mass of the underlying heart muscle. Thus, the R wave was found to be largest over the right ventricle, although its thickness was much less than that of the left ventricle. On the other hand, there was good correlation with spatial vectorcardiograms constructed from leads taken in a frontal and horizontal plane. The presence of a tall R wave over the right ventricle was compatible with the direction of the vector loop in the dog's heart. These observations failed to confirm the theory that the potential nearest to an exploring electrode is dominant in the genesis of an electrocardiographic pattern.

PICK

Sears, C. H., and Myers, G. B.: Diagnosis of Posterior Myocardial Infarction with the Aid of Semidirect Leads from the Back and Esophagus. Am. J. Med. **8:** 808 (June), 1950.

Large posterior myocardial infarcts may produce no diagnostic signs in standard leads and aV_F when the heart is in horizontal position. Infarcts confined to the basal portion of the posterior wall may be undetectable in these leads even though left ventricular potentials are referred to the diaphragm. The purpose of this study was to determine whether or not semidirect leads from the back would be of aid in the diagnosis of posterior infarction.

Nine back leads were obtained, namely, V_7, V_8, V_9 taken in the same transverse plane as V_5; V_6, HV_7, HV_8, HV_9 taken at the horizontal level at the junction of the third intercostal space and sternum and LV_7, LV_8, LV_9 taken at the level of the twelfth rib. These leads were obtained in 25 controls, in 36 patients with definite evidence of posterior infarction established either by autopsy or esophageal leads and in 12 additional patients in whom posterior infarction was established by previous serial electrocardiograms. The QRS-T pattern in the back leads has been correlated with that in the esophageal leads and in aV_F. Back leads were of aid in recognition and in estimation of the extent of the posterior infarct in many cases but failed to show definite signs of infarction in a few cases in which esophageal leads were positive.

AUTHORS

Joos, H. A., and Yu, P. N. G.: Electrocardiographic Observations in Poliomyelitis. Am. J. Dis. Child. **80:** 22 (July), 1950.

Electrocardiograms were taken on 23 patients with acute poliomyelitis shortly after hospital admission. Follow-up tracings were made within two to four days on those patients whose initial electrocardiogram was normal. If abnormalities were discovered, tracings were done at intervals until the electrocardiogram returned to normal. Fifty-five patients without evidence of cardiovascular disease were used as a control group. The only significant electrocardiographic abnormality was prolongation of the $Q\text{-}T_c$ interval, which occurred in 5 (21.7 per cent) of the 23 patients. The $Q\text{-}T_c$ interval was equivocal in 3 patients (13.0 per cent), and in 3 (5.4 per cent) of the control group. The difference in the $Q\text{-}T_c$ interval between the group with acute poliomyelitis and the control group was considered statistically significant.

MARGOLIES

Milanovich, J. B.: Experimental Determination of Choice of Polarity of Vectors. Cinematographic Documentation. Arch. d. mal. du coeur **43:** 444 (May), 1950.

The author presents an experimental study for the determination of the correct polarity to be used in clinical vectorcardiography. Momentary and successive changes were produced in the electrical charge of an electrolyte and transmitted to a cathode tube. The movements of its ray, accurately reflecting the variations of potential within the electrolyte, were registered by cinematography. Any change of electronegativity was followed by an orientation of the vector loop to the right and in an upward and forward direction. Similar "loops of negativity" were obtained by direct vectorcardiography from the surface of the heart of various animals. Most investigators use such a polarity of the electrodes as to produce vector loops opposite in direction to those obtained in the author's experiments. In order to produce vector patterns corresponding to the true conditions in the electrical field of the heart, the polarity of the electrodes customarily used in clinical vectorcardiography should be reversed.

PICK

Ravin, A., Dressler, S., Bronfin, G., and Hurst, A.: Cardiac Arrythmias Produced during Right Heart Catheterization. Report of Two Cases of Transient Partial Right Bundle Branch Block. Ann. Int. Med. **33:** 174 (July), 1950.

Since the right bundle branch is in a region where an intracardiac catheter might impinge upon it, it is possible that in some catheterized patients a right bundle branch block might be produced. Since it can be recognized only by electrocardiography, its failure to report could only mean that routine

electrocardiograms are not being made as extensively as they should.

The pressure of the catheter on the endocardium cannot be assumed to have no detrimental effect. The heavier and more rigid the catheter, the more the danger. Where catheterization is done in damaged hearts, the danger of death from arrythmia is greatly increased. When the heart is depressed by organic disease, not only is the refractory phase of the muscle increased, but the refractory periods of adjacent areas may be very unequal; as a result conditions are ideal for the production of ventricular fibrillation by a premature impulse initiated by the catheter tip.

The safest place for the catheter tip is in the pulmonary artery. If the catheter must be left in place any length of time, the catheter should, if possible, be passed into the pulmonary artery. If it must be left in the right ventricle, it would seem imperative to have continuous electrocardiographic control of the procedure. An instance of death during catheterization is believed to have resulted from displacement of the catheter from the pulmonary artery to the right ventricle during exercise. Preliminary work indicates that quinidine and procaine might be of value in inhibiting the arrhythmias.

WENDKOS

Kroop, I. G., and Grishman, A.: The Variability of the Electrocardiogram in Congenital Tricuspid Atresia. J. Pediat. **37:** 231 (August), 1950.

The electrocardiographic observations in 6 patients with congenital tricuspid atresia are presented. Left axis deviation, present in 1 case at 2 weeks of age, is considered an important point in the diagnosis. However, 2 of the 6 patients, 1 with and 1 without transposition of the great vessels, did not have left axis deviation. The factor which determines left axis deviation in the standard leads is the tall R in aV_L and the deep S in aV_F. The P waves were tall and peaked in all cases, and were associated with atrial enlargement and hypertrophy. The authors suggest that the right atrium, because of its position in relation to the diaphragm, may affect the potential distribution to the chest by marked displacement and rotation of the left ventricle.

MARGOLIES

Rosenman, R. H., Pick, A., and Katz, L. N.: Intraventricular Block. Arch. Int. Med. **86:** 196 (Aug.), 1950.

A review of the literature dealing with defective intraventricular conduction is presented. The term intraventricular block seems more appropriate than the term bundle branch block, since intraventricular block includes the latter, as well as defective impulse transmission in the free walls of the ventricles. Intraventricular block is essentially an electrocardiographic diagnosis No symptoms can be related to the conduction defect itself; the symptoms are those of the underlying heart disease.

Intraventricular block commonly occurs in diseased hearts. Rarely, it can be a congenital anomaly of the conduction system associated with septal or other defects, and in a few cases it is an isolated abnormality. In more than 80 per cent of cases, the underlying basis is hypertensive vascular disease and arteriosclerosis. About 10 per cent of cases occur in chronic rheumatic heart disease. Intraventricular block has occasionally been associated with myocarditis due to diphtheria, acute rheumatic carditis, syphilitic gummas of the septum, subacute bacterial endocarditis, tumors of the myocardium, and trauma.

Intraventricular block is about three times as common in men as in women, and more than 80 per cent of the patients are over 50 years old. The prognosis after the appearance of intraventricular block is related to the underlying heart disease. The average survival after the discovery of left intraventricular block is one to two years, but there are many exceptions. The patient, not the electrocardiogram, must be evaluated in the presence of intraventricular block, and emphasis should be given to the realization that intraventricular block occurs in patients who may live many years after its appearance and in persons with no other evidence of heart disease. The initial confusion concerning the localization, the clinical significance and the over-all prognosis of intraventricular conduction disturbances is largely resolved in this discussion.

BERNSTEIN

Israel, G. H., and Mazzei, E.S.: Paroxysmal Ventricular Tachycardia with Atrioventricular Block. Schweiz med. Wchnschr. **80:** 954 (Sept.), 1950.

Among 35,000 electrocardiograms the authors found 25 instances of paroxysmal auricular tachycardia with A-V block. Analysis suggests that this type of cardiac irregularity represents a special clinical syndrome. It occurs only rarely during childhood and is found more frequently in men than in women. In contrast to more common forms of supraventricular tachycardia, this type was found more often in patients with heart disease, produced more marked symptoms, and the duration of attacks was usually prolonged. The ventricular action may be irregular due to variable degrees of A-V block as revealed by an electrocardiography, which is indispensable for correct diagnosis. Quinidine by mouth proved to be most effective in the treatment of this arrhythmia.

PICK

Axen, O., and Lind, J.: Electrocardiographic Recording in Angiocardiography with Synchronous Serial Photography at Right Angled Planes. Cardiologia 16: 61, 1950.

A method is described by which in the recumbent

patient synchronous angiocardiograms can be obtained in right and left anterior oblique position. A part of the exposure voltage is transmitted to an oscillograph, which records the time of exposure simultaneously with an electrocardiogram (in lead IV). By this method the dynamics of the heart can be followed during different parts of the heart cycle. With an exposure at the time of maximal systole, the quantity of residual blood in the ventricles can be roughly estimated. The possibility of timing exactly the appearance of dye in the various chambers and in the great vessels permits an accurate estimation of the circulation time.

PICK

Routier, D.: Clinical Considerations on Mitral Stenosis. Acta cardiol. **5:** 363, 1950.

The clinical course of mitral valvular disease can be divided into two stages. The first, a period of stabilization, is a crippling condition, producing few symptoms, but restricting the patient in his activities. The second stage, the period of evolution, is the stage of complications like pulmonary edema, auricular fibrillation, embolization, and decompensation, and is, from the author's viewpoint, due to the addition of an inflammatory myocardial factor. Signs indicating the presence or approach of the latter stage are slight attacks of fever and elevation of the sedimentation rate. The infectious etiology of complications of mitral valvulitis should be considered in the clinical diagnosis and in the plan of treatment, especially before any attempt at a surgical approach to the disease.

PICK

Denolin, H.: Paroxysmal Ventricular Tachycardia Produced by Exercise in a Case of Auriculoventricular Dissociation. Acta cardiol. **5:** 425, 1950.

The author reports the case of a 60 year old man with arteriosclerotic heart disease and complete A-V block in whom on two occasions exercise produced transient paroxysmal ventricular tachycardia. The auricular rate rose during the attack from 90 to 165, while the rate of the ventricles changed from 38 to 107, coinciding with a change in direction of the QRS complex. On one occasion, reversion to the original rhythm occurred over a short period of ventricular bigeminy. The author considers the possibility that in the presence of arteriosclerotic heart disease, additional ventricular foci may be activated by ischemia following an exercise test.

PICK

Selvini, A., Pilotti, A., and Lanza, F.: Vectorial Study of Electrocardiographic Leads. Cardiologia **16:** 92, 1950.

The authors applied simple diagrams to the calculation of the vectors of various leads used in current electrocardiography. The orientation of these vectors in the frontal plane depends—in normal subjects—on the anatomic position of the heart and may change from subject to subject. The triangle formed by the 3 standard leads is not equilateral, since the direction of lead I is inclined at a certain angle to the horizontal. Wilson's central terminal lead also produces some deviations of the vector from the direction in which the lead is taken. The author presents a formula according to which this deviation can be avoided by increasing the resistance within the connections to the left leg and to the right arm. The results obtained by these studies confirm the validity of the theory of the summation vector.

PICK

Benchimol, A. B., Schlesinger, P., and Cotrim, M. R.: The Use of Multiple Esophageal Leads in Localizing and Evaluating Extension of Posterior Myocardial Infarction. Cardiologia **16:** 37, 1950.

The authors studied by multiple esophageal leads 11 cases in whom the presence of posterior myocardial infarction was suggested by the usual standard and unipolar leads and/or by a positive clinical history. In addition, the configuration of the normal esophageal electrocardiogram was studied in 3 subjects with particular reference to the QRS complex at the atrioventricular junction. An extensive and complete (transmural) infarction of the posterior wall produced a QS pattern in all leads taken at ventricular levels. A QR pattern over these areas indicates extensive but not transmural infarction. Multiple esophageal leads from various ventricular levels should always be taken, since an incomplete exploration may occasionaly fail to reveal localized lesions on the posterior wall. Although posterior wall infarction can usually be recognized in the standard leads or a unipolar lead from the left leg, there are instances in which esophageal potentials may be required for a positive diagnosis, as in high posterior infarction or in cases in which the position of the heart prevents the transmission of potentials of the infarcted area to the left leg.

PICK

Masini, V., Comberiati, L., and Puddu, V.: A Study of the P Wave of the Electrocardiogram before and following Auricular Fibrillation. Acta cardiol. **5:** 389, 1950.

The authors studied the contour of the P wave in 45 patients before and after transient auricular fibrillation. Cases with mitral heart disease always showed anomalies of P; 75 per cent of these consisted of widening to more than 0.11 second, increase in voltage and a characteristic contour in the chest leads (diphasic in V_1 and V_2, upright and notched in V_5 and V_6). In patients with arteriosclerotic heart disease similar changes were found; however, they were present less often and were less marked. In cases with clinically normal hearts

which developed paroxysmal auricular fibrillation, the P wave was normal preceding as well as following an attack.

The authors present an electrophysiologic explanation for the differences in P wave patterns in the three groups, based on the principles of direction, projection, and balance of vectors developed in normal and hypertrophied auricles. In patients with mitral heart disease, impending auricular fibrillation can be predicted if the P waves show marked alterations. In patients with arteriosclerotic heart disease the onset of fibrillation cannot be prognosticated due to the frequent lack of significant P wave changes.

PICK

Lepeschkin, E.: Electrocardiographic Observations on the Mechanism of Electrical Alternans of the Heart. Cardiologia **16:** 278, 1950.

In studying the effect of epinephrine and norepinephrine upon the cat heart, the author observed different types of electrical alternation which could be classified from an electrophysiologic standpoint into three groups. The first type, characterized by an alternation of QRS contour and a secondary alternation of S-T and T, can be explained by alternation of the sequence of electrical activation of the heart muscle. This may be effected either by an alternating delay of conduction or by alternating partial premature contraction (pre-excitation). The second type consisted of (primary) alternation of displacement of the S-T segment and of the direction of the T wave, without appreciable alteration of the QRS. This type is ascribed by the author to an alternation of "possession," i.e., of the degree and extent to which the heart muscle responds to stimulation. The third type, alternation of regression or restitution, is characterized by alternation of the duration of the T wave and of the Q-T interval. This was seen with abrupt changes of the heart rate and could be correlated with the duration of the diastolic pause. The author discusses the possibility of a fourth type, namely alternation of the amplitude of QRS and T due to changes in distribution of electrical potentials in association with mechanical alternation.

PICK

Pick, A., and Fishman, A. P.: Observations in Heart Block. Supernormality of A-V and Intraventricular Conduction and Ventricular Parasystole under the Influence of Epinephrine. Acta cardiol. **5:** 270, 1950.

The authors report electrocardiographic observations in a 25 year old woman with syphilitic heart disease and almost complete atrioventricular block. Conduction of sinus impulses occurred when a sinus P wave preceded or followed at a short interval an automatic beat. The QRS of the automatic beats was of normal duration in contrast to the QRS of the idioventricular pacemaker, the origin of which could be located above the bifurcation of the common bundle.

In the course of various pharmacologic tests, an additional ventricular parasytolic pacemaker was activated by epinephrine, which, similar to the original supraventricular pacemaker, initiated single instances of A-V conduction. The authors assume the presence of a supernormal phase of both A-V and intraventricular conduction and a facilitating effect (Skramlik's "Bahnung") of retrograde impulses from both pacemakers upon A-V conduction. The liberation of an additional ventricular pacemaker by epinephrine indicates that the use of sympathomimetic drugs may be dangerous in cases in which one ectopic pacemaker is already in action.

PICK

Groedel, F. M., and Miller, M.: The Duration of the Ventricular Systole. Cardiologia **16:** 269, 1950.

Electrical ventricular systole is not identical with the mechanical systole. According to previous investigations of the authors, the beginning of the mechanical systole coincides with the peak of the S wave in a chest lead, the distance R-S being variable. Furthermore, the second sound, indicating the end of ventricular ejection, may, in the experience of the authors, occur any time between the formation of peak of the T wave or 0.12 second later. The authors feel that the clinical value of the relation of electrical systole to electrical diastole, determined from a limb lead electrocardiogram, and the various formulas recommended for such calculations are questionable. Instead, they recommend the determination of "hemodynamic systole," defined as the distance between the peak of S wave to the onset of the second sound. This value can be readily determined by simultaneous registration of a precordial lead and a phonocardiogram from the base of the heart.

PICK

v. Skramlik, E.: The Experimental Production of Wenckebach Periods. Cardiologia **16:** 361, 1950.

It is possible to produce in the exposed frog heart (*Rana temporaria*) by moderate electrical stimulation of the vagus nerve typical Wenckebach periods, which consist of progressive prolongation of the conduction time between atrium and ventricle or between sinus venosus and atrium. This effect can be promptly abolished by brief perfusion of the heart with Ringer's solution. It appears that following vagus stimulation, the heart loses its ability to destroy acetylcholine which accumulates in the tissues, especially the conduction system, and affects the refractory period of the latter. However, the fixation of the vagus substance to the muscle cells seems to be only a loose one as evidenced by the

prompt restitution of normal rhythm following perfusion.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Scheinberg, P.: Cerebral Circulation and Metabolism in Hyperthyroidism. J. Clin. Investigation **29:** 1010 (Aug.), 1950.

Cerebral blood flow and oxygen consumption were studied in 9 patients with hyperthyroidism who were irritable, nervous, and emotionally labile. The cerebral blood flow, mean arterial-cerebral venous oxygen difference, oxygen consumption, vascular resistance, and cerebral venous oxygen tension were all within normal limits. Since no effective means of increasing cerebral metabolism in man has been found and since apprehension fever and thyrotoxicosis do not increase cerebral metabolism, it is suggested that cerebral metabolism normally functions at nearly its maximal rate, and it appears that the psychic manifestations which occur in hyperthyroidism are not related to increased metabolism of the brain.

WAIFE

HYPERTENSION

Cier, J. F.: On Suprarenal Ischemia as a Factor Producing Hypertension. Compt. rend. Soc. de biol. **144:** 533 (April), 1950.

Repeating experiments described previously by Victor, the author studied in 4 dogs the effect of ischemia of one suprarenal gland upon the blood pressure. Isolation of the left adrenal from its blood supply was achieved by double ligation of the vessels or by complete dissection of the organ from the surrounding tissues. The presence of ischemic changes was proven histologically in one animal, which was sacrificed 15 days following operation. All of the animals remained normotensive during an observation period up to 14 months. The experiments failed to confirm the role of suprarenal ischemia in the production of experimental hypertension, as claimed in the literature.

PICK

Bartels, E. C., and Cattell, R. B.: Pheochromocytoma: Its Diagnosis and Treatment. Ann. Surg. **131:** 903 (June), 1950.

The authors describe 4 cases of pheochromocytoma diagnosed clinically and successfully removed. These were associated with the following symptoms: (1) vasomotor manifestations in the form of palpitation, sweating, and blotchiness of the skin, (2) substernal pain with dyspnea simulating angina pectoris, (3) occipital headache, (4) blindness and symptoms of toxemia occurring early in pregnancy. The clinical findings in these cases were sustained hypertension in 1 case, hypertensive crises in 2 cases, and mild fluctuant hypertension in 1. The basal metabolic rate was elevated in all either during or before and after the attacks. Intravenous pyelograms were sufficiently abnormal in 3 cases to indicate the site of the tumor. Abnormal blood sugar levels were observed in 3 cases. The specific diagnostic tests with histamine, Etamon, Mecholyl, and Dibenamine were helpful, but not entirely specific. A negative test with any one of these agents did not rule out pheochromocytoma.

The authors recommend ethylene-ether or cyclopropane-ether anesthesia administered endotracheally. They warn against the use of fluids and cortical extracts to combat surgical shock during the procedure. The hypertensive reaction during manipulation of the tumor may be countered by the use of adrenolytic drugs. Many of the shock-like syndromes seen are due to acute left ventricular failure due to the hypertensive reaction. Exploration of both sides is necessary, because in 10 per cent of the cases tumors are bilateral, and because there may be congenital absence or atrophy of the contralateral adrenal gland.

KLOSK

Cole, L.: The Early Diagnosis of Pheochromocytoma. Brit. Heart J. **12:** 232 (July), 1950.

The author reports the clinical and pathologic findings in a patient with pheochromocytoma. He believes that the sudden onset of headache preceding the rise in blood pressure, periodic morning and evening headache, upper abdominal paresthesias with sinking spells, and slow increase in intensity of symptoms without rise in blood pressure should raise suspicion of the presence of this lesion. Tests suggestive of hypersecretion of adrenaline are (1) massage of the tumor region with production of an attack, (2) the use of benzodioxanes to lower the blood pressure, (3) intravenous injection of histamine to produce an attack, (4) visualization of the kidneys or perirenal insufflations with oxygen, and (5) an increase in basal metabolism.

SOLOFF

Deterling, R. A., Jr., and Essex, H. E.: Experimental Renal Hypertension and its Course following the Production of a Peripheral Arteriovenous Fistula. Ann. Surg. **132:** 129 (July), 1950.

The authors studied the effect of a femoral arteriovenous fistula on the course of experimentally induced renal hypertension in 19 dogs. Arterial blood pressure was measured directly in the femoral artery of the unanesthetized trained dog, using the Hamilton manometer. Hypertension was produced by wrapping the kidney in silk. No permanent lowering of the blood pressure occurred as a result of the existence of the arteriovenous fistula. The cardiovascular alterations were of greater magnitude than were observed from either the hypertension or the

fistula alone. The mortality was higher and the pathologic changes more widespread.

ABRAMSON

Rather, L. J.: The Pathogenesis of Hypertension Induced by Renal Constriction. J. Exper. Med. **92:** 59 (July), 1950.

The author attempted to clarify the following problems: the time of onset of hypertension after the one-stage operation of unilateral nephrectomy and contralateral renal constriction by the Grollman technic; the relation of the amount of functioning renal tissue to the development and degree of hypertension and the effect of this constriction on renal growth, with and without contralateral nephrectomy.

After basal blood pressure levels were determined on 42 young male albino rats, they were divided into four groups and subjected to one of the following operations: (1) unilateral nephrectomy with exposure and handling of the opposite kidney; (2) unilateral nephrectomy and constriction of the remaining kidney with a silk figure-of-eight ligature; (3) unilateral renal constriction with a silk figure-of-eight ligature, the other kidney being left intact after exposure and handling and (4) unilateral nephrectomy with removal of the poles of the contralateral kidney.

For 50 days following operation a significant increase in blood pressure developed in the group subjected to the second type of operation, starting within four days after operation. Hypertension did not develop in any of the other groups. The development of renal constrictive hypertension in rats was not believed due either to reduction in the total mass of functioning renal tissue, to the prevention of renal compensatory hypertrophy, or to the presence of fibrous perinephritis. The results were most compatible with the hypothesis that there is some disturbance of hemodynamics or of tissue tension with the liberation of a pressor substance by the affected kidney.

SCHWARTZ

Kipkie, G. F.: Possible Role of Infection in the Production of Periarteritis Nodosa in Hypertensive Rabbits. Arch. Path. **50:** 98 (July), 1950.

In a previous study medial arteriolar hypertrophy was a common finding in experimental hypertension in rabbits, particularly in the submucosa of the intestinal tract. Other viscera were affected to a lesser degree but showed the same pattern. Accidental infection in 3 rabbits was accompanied by the development of arterial and arteriolar lesions similar to those of periarteritis nodosa in man.

The author studied the possible role of infection in the production of such lesions in rabbits made hypertensive by unilateral nephrectomy and cellophane wrapping of the other kidney. Controls consisted of untreated rabbits and uninfected hypertensive rabbits. Infection in the third group was caused by inserting gauze soaked with *Staphylococcus albus* culture under the perirenal cellophane wrapping. In 100 days the normal animals showed no arteriolar changes. The uninfected hypertensive group revealed the medial arteriolar hyperplasia noted in the previous work. Two infected hypertensive rabbits in a group of 6 showed typical lesions of periarteritis nodosa.

The author discusses the relative importance of both hypertension and infection in the development of these lesions and reviews the theories of others, especially in reference to the sharpness of the ascent of the experimental hypertension and the sudden strain thrown upon vessel walls. However, his own rabbits showed their vascular lesions in the presence of only a moderate hypertension.

GOULEY

Trueta, J.: The Relation of Hypertension to the Renal Circulation. Glasgow Med. J. **31:** 217 (July), 1950.

The author reviews the experimental data showing that medullary circulation through the basal or juxtamedullary glomeruli might persist or even increase while the renal cortex is ischemic. The author suggests that under certain conditions the medullary bypass is a functional adaptation to stimuli which may vary from cold, emotion, or fatigue on the one hand, to "shock" on the other. In 2 human kidneys removed at autopsy from patients who died from shock, the medullary circulation was found to be exceedingly rich; the distribution of the intrarenal blood, judging by the caliber and easy injection of these vessels, was found to be reversed in its normal proportions.

It is suggested that in certain people the normally highly contractable arterioles of the renal cortex are frequently subjected to constriction, either by the sympathetic or by the hormonic complex. This fulfills the requirements for the production of renin, VEM, or other pressor substances or for the inhibition of antipressor substances by the renal cortex. Persistent repeated hypoxia of the cortex ends by producing sclerotic changes of the cortical vessels.

WAIFE

Koffler, I., Buck, G., Wingard, C., Hitchcock, P., Guthrie, R., and Teague, R. S.: A Case of Pheochromocytoma: Diagnosis by the Benzodioxane Test, Urinary Hormone Studies, and Nor-epinephrine Assay of the Tumor. J. Clin. Endocrinol. **10:** 897 (Aug.), 1950.

The authors report the case of a 12 year old Negro boy with known severe hypertension for two years, with episodes of coma, evidence of fundic, renal, and cardiac damage, and a left hemiplegia. A pheochromocytoma was diagnosed on the basis of a depressor response to benzodioxane and Dibena-

mine, and despite negative radiologic evidence, the patient was explored. A 6 by 4.5 cm. tumor was removed from the upper pole of the right kidney with the pathologic characteristics of a pheochromocytoma. Extracts of the tumor were assayed on dogs before and after Dibenamine, the results suggesting that 90 per cent of the pressor activity was due to norepinephrine, with 1 Gm. of tumor equivalent to the activity of 0.86 mg. of d,l-norepinephrine. By the method of paper chromatography, the activity of 1 Gm. of tumor was determined as equivalent to 1.04 mg. of d,l-norepinephrine. Small amounts of epinephrine were also present. Following surgery the patient showed improvement in all signs and symptoms and a normal blood pressure.

CORTELL

White, P. D., Dimond, E. G., Williams, A.: Follow-up Study of One Hundred Private Hypertensive Patients with Cardiovascular Complications. J.A.M.A. **143:** 1311 (August), 1950.

The authors report on 50 hypertensive patients treated by lumbodorsal sympathectomy in the years 1941 to 1946. A control group of 50 hypertensive patients in the same age range, who were not subjected to sympathectomy, was used for comparison. All the patients had the same interrogator and examiner during the study. The 50 sympathectomies were all performed by the same surgeon and by one technic. All cases were seriously affected by hypertension as shown by the presence of some important cardiovascular complication such as myocardial insufficiency, cerebral vascular accident, past myocardial infarction, or angina pectoris. Patients with renal insufficiency were excluded from the study. The sympathectomized patients included 38 men and 12 women; the control cases included 37 men and 13 women. After a three year follow-up of the sympathectomized patients, the result was excellent or good in 11; fair with definite (though not decided) improvement in 11; little or no change in 5; 11 patients were worse, and 12 were dead. Among the controls only 1 patient continued to be in good condition, 4 were unchanged, and 41 were worse or dead.

KITCHELL

Clinico-Pathologic Conference: Renal Insufficiency. Am. J. Med. **9:** 247 (Aug.), 1950.

A discussion is presented of a fatal case of chronic glomerulonephritis in a hypertensive man 23 years of age who had previously had rheumatic fever and acute glomerulonephritis. These diseases were considered to be diseases of hypersensitivity. They occur together in 1 to 2 per cent of cases. The anemia associated with renal insufficiency is attributed mainly to the insufficient production of red blood cells, although in some patients at certain times an extracorpuscular hemolytic factor may operate. In patients with normal or mild hypertension, the transfusion of hypertensive blood leads to little or no change in blood pressure or renal hemodynamics, but hypertensive blood administered to patients with severe renal disease causes their blood pressure to rise to higher levels than prior to transfusion.

HARRIS

Vancura, F.: On Transient Hypertension in Young Subjects. Cardiologia **16:** 124, 1950.

The author reports a 20 year follow-up study of 448 young individuals with transient blood pressure elevation of more than 30 mm. Hg. The cases were divided into 3 groups (15 to 24 years, 25 to 34 years, and 35 to 44 years of age) according to the age at which the pressure elevation was first noted. After 20 years, hypertension was found in 43 per cent of group I, in 60 per cent of group II, and in 51.8 per cent of group III. The author concludes that transient hypertension is of significance in all age groups, especially in middle age, in which it represents an early sign of hypertensive disease. An elevated blood pressure found during puberty led to permanent hypertension in more than 40 per cent of cases.

PICK

PATHOLOGIC PHYSIOLOGY

Hamilton, W. F., Jr., Dow, P., and Hamilton, W. F.: Measurement of Volume of Dog's Heart by X-ray: Effect of Hemorrhage, of Epinephrine Infusion, and of Buffer Nerve Section. Am. J. Physiol. **161:** 466 (June), 1950.

A new formula and nomogram are given for the calculation of the volume of dog's heart from the area of its shadow in an anteroposterior x-ray film. Data concerning this area-volume relationship were obtained empirically from 61 normal dogs.

Changes in heart volume were observed (1) during a stepwise hemorrhage with or without pretreatment with Dibenamine, (2) on bleeding during epinephrine hypertension. The reduction in heart size after hemorrhage was striking and in some instances amounted to one-fourth of the total lethal bleeding volume. Epinephrine increased the heart volume in these experiments, but an equal hypertension produced by section of the buffer nerves was not followed by a significant volume change. The heart volume changes may account for a large part of the intrathoracic blood volume changes calculated from dye injection methods.

HECHT

Ian, A., and Maitland, L.: The Effect of Splanchnicectomy on Renal Function. Lancet **2:** 7 (July), 1950.

The author believes that part of the benefit derived from bilateral splanchnicectomy in hypertension may be due to some redistribution of the blood flow within the kidney. Inasmuch as such an effect would be demonstrable by an alteration in the

urine obtained before and after the operation the author undertook this study.

Complete renal analysis was made on each patient before and after surgery. In four of the 7 patients studied, sympathectomy produced an improvement in the standard urea clearance of the denervated kidney. In 3 cases, an increased volume of urine was obtained, which he believes was evidence for an increase in the number of nephrons brought into action. Besides the increase in urinary volume in these, an increased urea content indicated improvement of tubular function. In 2 of the patients evidence of increased renal blood flow followed surgery. In 5 cases followed over a year's period, renal function was well correlated with the late result of treatment.

TANDOWSKY

Finch, S., Haskings, E., and Finch, C. A.: Iron Metabolism. Hematopoiesis following Phlebotomy. Iron as a Limiting Factor. J. Clin. Investigation **29:** 1078 (Aug.), 1950.

In anemia produced in dogs and man by repeated phlebotomy, the rate of blood regeneration depended chiefly on available body storage of iron. The removal of 3500 ml. of blood in normal subjects over a period of seven weeks led to a retardation of hematopoiesis if the subjects were on a diet without supplemental iron. In patients with excessive tissue iron, including those with hemochromatosis, blood production continued at an accelerated rate, and weekly phlebotomies of 500 ml. could be continued for months without a development of significant anemia.

WAIFE

PATHOLOGY

Hesse, H.: Contributions to the Hypertrophy of the Heart. Ztschr. f. d. ges. inn. Med. **5:** 135 (March), 1950.

The author studied the histologic picture of the left ventricle in 3 normal subjects and in 7 patients with moderate to marked cardiac hypertrophy. Of the latter, 3 also had marked dilatation of the chamber. The increase in size of the muscle fibers, characteristic of hypertrophy, was more marked in sections taken from the apical region than in sections from the basal parts of the ventricle. On the other hand, myofibrosis, which accompanies dilatation, was found only in the basal myocardium and was absent in sections taken from the apex.

These histologic findings are in accord with the roentgenologic picture of elongation of the outflow tract of the left ventricle in early hypertrophy and of rounding of the contour of the left ventricle in the presence of dilatation. The characteristic changes of the electrocardiogram, S-T depression and T wave inversion, could be demonstrated in each of the 7 cases with hypertrophy in a bipolar chest lead, with one electrode over the base and the other over the apex of the heart.

PICK

Atlas, D. H., Gaberman, P., and Stern, K.: Primary Amyloidosis Associated with Hyperlipemia and Hypercholesterolemia. Am. J. Clin. Path. **20:** 371 (April), 1950.

The authors report a case of primary amyloidosis associated with hypercholesterolemia and hyperlipemia. The patient for several years had had signs of congestive heart failure which did not respond to the usual type of treatment. Albuminuria had been present for 25 years. The Congo red test was interpreted as normal. Clinically the liver was found to be markedly enlarged, and the spleen was easily palpable. The serum was persistently milky and rich in cholesterol. At autopsy the liver, spleen and kidneys were found to be considerably enlarged. Microscopic examination revealed amyloidosis of these organs.

ABRAMSON

Daugherty, G. W., and Baggenstoss, A. H.: Syndrome Characterized By Glomerulonephritis and Arthritis; Libman-Sacks Disease with Predominantly Renal Involvement. Arch. Int. Med. **85:** 900 (June), 1950.

The authors report 6 cases of a syndrome characterized by arthritic and periarthritic manifestations, followed by a diffuse generalized disease in which a glomerulonephritis with the nephrotic syndrome is the central feature. In all instances of the syndrome observed, the outcome was rapidly fatal once the nephrotic picture became manifest. The pathologic and bacteriologic studies failed to reveal a specific bacterial or viral agent. The authors suggest designating all these cases as Libman-Sacks disease, leaving lupus erythematosus as the designation of the characteristic lesion of the skin. It is a nondescriptive term which may be dropped as soon as the cause for the disease is determined and a name based on cause can be substituted. The term "lupus erythematosus" implies primarily a disease of the skin, which it almost certainly is not. There is no good evidence of any relation between this disease and tuberculosis, thus making the term "lupus" misleading. It obviates the necessity of using the ambiguous, incomprehensible term "lupus erythematosus sine lupo."

The findings of the authors suggest, but do not permit the conclusion, that a hyperergic state may be an important factor in the Libman-Sacks syndrome.

BERNSTEIN

PHARMACOLOGY

Charlier, R., and Philippot, F.: The Prevention by Khellin of Ventricular Fibrillation Induced by Chloroform-Adrenaline Technic. Arch. internat.

de pharmacodyn. et de therap. **81:** 404 (March), 1950.

Khellin produces an arterial hypotension which counteracts the hypertension produced by injection of adrenaline in dogs given chloralosane. The hypotensive effect is very short and is believed due to its relaxing effect on smooth muscle of the blood vessels. It seems to be independent of the carotid sinus and aortic-cardiac reflexes. Khellin is also a coronary vasodilator. Some investigators believe this effect is responsible for prevention of chloroform-adrenaline ventricular fibrillation. The authors studied this matter with experiments in 14 dogs. In 10 of 12 experiments, khellin prevented the induction of ventricular fibrillation by chloroform and adrenaline. Five dogs developed fatal ventricular fibrillation when given adrenaline intravenously during chloroform anesthesia without khellin. This antifibrillatory action of khellin differed from that seen when caffeine and amyl nitrite were used. The latter drugs were able to prevent the hypertensive effect of large doses of adrenaline, but khellin was not. Therefore, this antifibrillatory action seems to be independent of the adrenaline hypertension. This suggests that khellin may also prevent ventricular fibrillation by stopping the initiation of adrenaline-induced cardiac ectopic rhythms.

LECKS

Marx, H., and Hasse, H.: The Effect of Diethylaminoethanol on the Circulation (a Contribution to the Effect of Novocain). Ztschr. f. Kreislaufforsch. **39:** 206 (April), 1950.

The authors studied the effect of diethylaminoethanol, a vasoactive derivative of novocain, upon the circulation of 15 normal persons, 2 subjects with acroparesthesia, and 3 patients with endangiitis obliterans. The changes occurring following intravenous injection of the drug were analyzed according to the method of Broemser and Ranke. The skin temperature was measured thermoelectrically.

The usual result was a decrease in blood pressure and cardiac output and an increase in peripheral resistance and skin temperature over peripheral parts of the extremities. This would suggest, that diethylaminoethanol produces a passive hyperemia of the extremities, due to an accumulation of blood in the blood depots, mainly in the subpapillary plexus of the skin.

PICK

Frischknecht, W.: Normalization of the Electrocardiograms and Decrease of Leukocytosis through the Sympatholytic Action of Hydergin (Sandoz) in the Presence of Pertussis. Helvet. paediat. acta **5:** 120 (May), 1950.

In infancy and childhood, a sympathetic tone unfavorable to the myocardium can be diagnosed with the aid of the ergot derivatives dihydroergotamine (D.H.E.) or Hydergin.

1. The electrocardiograms of 5 out of 18 healthy infants without pertussis showed significant changes 30 minutes after subcutaneous administration of D.H.E. (0.005 mg. per Kg.): normalization of flattened T waves, decrease in tachycardia, and disappearance of auricular and ventricular extrasystoles. These 5 infants showed a change in skin color, acrocyanosis, and a tendency toward convulsions and vomiting.

2. Flattened T waves in 20 infants and children with pertussis were brought to normal level in 6 cases by Hydergin (0.01 mg. per Kg.). The angle between the greatest R and T vector was thereby reduced an average of 35 per cent. These 6 cases all showed the severest attacks of either apnea, cyanosis, or pneumonia.

3. An individual sensitivity to the ergot preparations exists in infancy and childhood. Paradoxically, the sympatholytic Hydergin can temporarily increase the sinus rate, flatten the T waves, and in cases with cerebral lesions revert a paroxysmal tachycardia. In the Hydergin-refractory cases we are dealing with either uncomplicated, mild cases of whooping cough (electrocardiogram normal) or with severe clinical cases (mostly with pathologic T waves).

Hydergin (0.01 mg. per Kg. by subcutaneous injection) in cases of pertussis lowers the leukocytosis in the peripheral blood on the average of 16 per cent within 45 minutes. (In the electrocardiogram, the angle between the vector R and the vector T is at the same time lessened on the average about 14 per cent; the sinus rate only about 5 per cent.) No obligatory connection exists between the normalization of the electrocardiogram and the influence of Hydergin on the leukocyte count.

AUTHOR

Enselberg, C. D., Simmons, H. G., and Mintz, A. A.: The Effects of Magnesium Upon Cardiac Arrhythmias. Am. Heart J. **39:** 703 (May), 1950.

The authors studied the influence of magnesium upon various arrhythmias, particularly those associated with digitalis administration and definite digitalis intoxication. Magnesium sulfate was given intravenously (20 cc. of a 20 per cent solution) 29 times to 25 patients with a variety of rhythmic disturbances. Injection was completed within 10 seconds, and continuous electrocardiographic observations were made for the first one or two minutes after the start of injection and at short intervals thereafter. The cardiac effects were rapid in onset and lasted rarely more than eight minutes. Ventricular extrasystoles were diminished in number or abolished in 13 of 14 cases. Often magnesium caused a transient increase in their frequency, and occasionally extrasystoles from new foci appeared for a few

seconds. In one case, there was a short run of bidirectional ventricular tachycardia. Sinus arrests due to digitalis intoxication were sharply, though transiently, abolished in 2 cases. The effects of magnesium were not uniform in auricular flutter and fibrillation. In 2 of 5 patients with auricular fibrillation, the ventricular rate slowed significantly, from 88 to 50 in one patient, and from 66 to 20 in the other. The therapeutic use of magnesium in arrhythmias is limited by its ephemeral action and by its occasional undesirable effects.

HELLERSTEIN

Enselberg, C. D., Simmons, H. G., and Mintz, A. A.: The Effects of Potassium upon the Heart, with Special Reference to the Possibility of Treatment of Toxic Arrhythmias Due to Digitalis. Am. Heart J. **39:** 713 (May), 1950.

The authors studied the effects of oral potassium salts (2 to 10 Gm.) on a variety of arrhythmias due to digitalis intoxication in 27 of 31 patients. Electrocardiograms were made before the ingestion of potassium and at intervals of 30 to 60 minutes thereafter. Serum potassium was not determined. Effects occurred within one half hour and persisted at least 4 hours. Ventricular extrasystoles were abolished or greatly diminished in each trial. Sinus rhythm was restored in 2 patients with auricular tachycardia within 30 minutes after the administration of potassium. In patients with auricular flutter, fibrillation, and incomplete heart block, the ventricular rate decreased. In 2 patients, periods of sinus arrest occurred more frequently after potassium. There were no significant changes in the T wave or RS-T segment. Since toxic effects of digitalis are associated with a loss of potassium from the myocardium, the abolition of associated arrhythmias (ventricular tachycardia, ventricular extrasystoles) may be due to the replacement of this deficient ion in the heart muscle.

HELLERSTEIN

Wallner, A., and Herman, L.: Mercurial Diuretics: Some Hazards of Mercuhydrin. Report of Two Cases with One Death. Ann. Int. Med. **32:** 1190 (June), 1950.

A 50 year old man with congestive failure daily received 2 cc. of Mercuhydrin intramuscularly. On the eighteenth hospital day, within 30 minutes after injection, the patient complained of severe pains in his eyes, head, and lumbar region. This was followed by generalized tingling, dyspnea, nausea, vomiting of a large amount of blood-tinged fluid, pains in the chest, and blanching of the feet. Five hours after injection, he went into profound shock and died. At necropsy there was striking pallor of the renal cortex and extreme vascularity of the medullary portion. The glomeruli were pale, bloodless, and swollen so that Bowman's capsular space was very narrow. There was extensive necrosis of the proximal convoluted tubules. It is believed that death was due to an anaphylactic reaction.

A second patient, a 56 year old man with pulmonary and peripheral edema resulting from rheumatic heart disease, was also given 2 cc. of Mercuhydrin intramuscularly daily. On the tenth and eleventh hospital days, he complained of weakness and dizziness, and a temperature rise of 4 F. was noted. Mercuhydrin was withheld until the fourteenth hospital day. Within an hour after injection he complained of nausea and headache, followed by vomiting, coughing, chills, and slight cyanosis. He became restless and confused; his temperature rose to 104.6 F., and his pulse rate to 140, accompanied by disorientation and marked flushing. This was followed by incontinence of urine, generalized twitchings, and clonic contractions of all extremities. He became comatose but gradually recovered. Mercuhydrin was withheld for 11 days. Then a trial dose of 0.25 cc. was given. Within a half hour the patient complained of headache, vomiting, arthralgia, was again confused, and had a rise in temperature. The patient felt fairly well the following day. He was then given Mercupurin .05 cc. intramuscularly, which was doubled daily until 2 cc. was reached. Because there was no adverse reaction to Mercupurin, he was again tested with .05 cc. Mercuhydrin. Within 90 minutes he had a repetition of all the symptoms previously encountered. It was several days before he felt well. The reactions in this patient are thought to be allergic, because reactions did not occur following initial injections of Mercuhydrin, a severe reaction followed injection of 0.05 cc. of Mercuhydrin, and unfavorable reactions did not follow injection of 2 cc. of Mercupurin.

WENDKOS

Madison, L. L.: Comparison of the Anterior Pituitary-Adrenal Cortical Stimulating Effect of U.S.P. Epinephrine, Synthetic l-Epinephrine, and Nor-Epinephrine. J. Clin. Investigation **29:** 789 (June), 1950.

The author determined which of the medullary hormones in U.S.P. commercial epinephrine is responsible for the eosinopenia secondary to anterior pituitary-adrenal cortical stimulation. Three tenths cc. of U.S.P. epinephrine, synthetic l-epinephrine, and norepinephrine was injected into each of 15 normal fasting male subjects on different days. It was found that norepinephrine had no effect on total circulating eosinophils. This indicated that the anterior pituitary-adrenal cortical stimulating effect of U.S.P. epinephrine is attendant on its l-epinephrine content, and not on the norepinephrine which is present.

WAIFE

Lehman, R. A., King, E. E., and Taube, H.: The Pharmacology of Thiomerin. J. Pharmacol. & Exper. Therap. **99:** 149 (June), 1950.

The pharmacologic properties of a new, effective mercurial diuretic, Thiomerin, in which the theophylline residue is replaced by a monothiol, are discussed. The acute cardiotoxic effects, as measured by acute lethal doses in cat, isolated cat heart, rabbit, and mouse, are many times lower than that of other mercurial diuretics. In its more chronic effects, the toxicity of Thiomerin is comparable to that of Mercuzanthin and Mercuhydrin. The absorption of Thiomerin from muscle is slightly, but not significantly, more rapid than that of other mercurials, and the urinary excretion of mercury is likewise similar to that observed after the administration of Mercuzanthin and Salyrgan-theophylline.

GROSSMAN

Johnstone, M.: Cyclopropane Anaesthesia and Ventricular Arrhythmias. Brit. Heart J. **12:** 239 (July), 1950.

Ninety patients were investigated during cyclopropane anesthesia by constant observation of an electrocardiogram. A record was made of all arrhythmias. The effects of (1) hypoxia, (2) hypoxia and carbon dioxide accumulation, (3) hyperventilation and carbon dioxide accumulation, and (4) hyperventilation and deep anesthesia were studied. The author concludes that carbon dioxide accumulation precipitates ventricular arrhythmias during cyclopropane anesthesia, possibly by a sympathomimetic effect which liberates adrenaline that produces cardiac irregularities. There is no difference in incidence of ventricular premature beats in individuals with normal and those with abnormal hearts. Ventricular arrhythmias due to cyclopropane can be prevented by assisting respiration to insure an adequate intake of oxygen and output of carbon dioxide. Irritant gases such as ether cause reflex vagal inhibition of the heart by stimulation of vagal receptors in the air passages which inhibits the ectopic centers in the ventricles.

To prevent cyclopropane arrhythmias, the various factors that lead to carbon dioxide accumulation must be avoided. One should avoid pre-operative sedation, assist respiration, cocainize air passages, use fresh soda-lime, and pay careful attention to the unidirectional valves of the apparatus.

SOLOFF

Kappert, A., Sutton, G. C., Reale, A., Skoglund, K. H., and Nylin, G.: The Clinical Response of Human Beings to l-Nor-adrenaline and Its Clinical Applicability. Acta cardiol. **5:** 121, 1950.

The authors injected by slow intravenous drip (0.007 to 0.02 mg. per minute) Arterenol (noradrenaline) into young, healthy individuals and made the following observations:

Noradrenaline produced a marked increase of both systolic and diastolic blood pressure without changing the pulse pressure. At the same time, a decrease in skin temperature and a drop in pulse rate were noted. The latter could be prevented by atropine. The degree of blood pressure elevation and bradycardia was proportional to the amount of Arterenol injected. Hydergin reduced the elevated blood pressure to normal and, if injected preceding the experiment, prevented elevation. A change in the distribution of blood constituents was indicated by an increase of the hematocrit with no change in circulating blood cell volume. The electrocardiogram showed significant alterations. In contrast to adrenaline, Arterenol did not affect the basal metabolic rate and produced only a small and transient elevation of the blood sugar level.

The authors conclude that noradrenaline has a marked vasoconstrictor and hypertensive effect, has no marked metabolic properties, and does not influence the activity of the heart. It is of value in the treatment of certain types of shock, especially in diabetics. It should not be used in oligemic shock, since the study of its action reveals "a withdrawal of a portion of plasma from the actively circulating blood stream."

PICK

Keith, N. M., Power, M. H., and Daugherty, G. W.: The Action of Cortisone in Nephritis With Edema. Proc. Staff Meet. Mayo Clin. **25:** 491 (Aug.), 1950.

A study of some effects of cortisone acetate was carried out on 5 patients with acute, subacute, or chronic glomerulonephritis. They all exhibited varying degrees of edema, hypoproteinemia, and considerable excretion of protein in the urine. In 3 cases the nephrotic features predominated, while in 2, general anasarca was accompanied by azotemia.

The administration of cortisone in doses of 50 to 100 mg. a day for 12 to 20 days to the 3 edematous patients produced definite effects on the body weight and renal excretion of water, salt and protein. In the first few days there was a noticeable increase in weight and in proteinuria, accompanied by a decreased excretion of water, chloride, and sodium. Within a week to 10 days this period of retention of fluid and salt was replaced by one of loss of weight, diminished protein excretion and saline diuresis. The diuresis finally led to disappearance of the edema. A metabolic effect on intracellular metabolism was indicated by an increase in the urinary nonprotein nitrogen and a simultaneous rise in the concentration of urea in the blood. The hypoproteinemia of a single patient was restored to normal. In 1 of the 3 patients with nephrotic edema diuresis was accompanied by a distinct rise in the concentration of urea and potassium in the blood such as is observed in early azotemia. This suggested renal insufficiency. In 2 patients who had chronic glomerulonephritis, edema and azotemia, cortisone increased proteinuria and the formation of nitrogenous waste products. It failed to alter renal func-

tion or to bring about diuresis. The azotemia increased and hyperpotassemia resulted.

SIMON

PHYSICAL SIGNS

Ungar, H., and Ullmann, Th.D.: Acquired Defect of the Intraventricular Septum of the Heart. Cardiologia **16:** 67, 1950.

A 60 year old woman, from whom no history could be obtained, presented a loud systolic murmur over the entire precordium and in the electrocardiogram right axis shift and inversion of T in leads II, III and CF_4. The patient died in congestive heart failure after 14 days of observation. The autopsy revealed a funnel-shaped perforation within an area of healed infarction of the intraventricular septum. In addition, a recent posterior wall infarct was also found. The authors discuss the anatomic and clinical features of an acquired defect of the intraventricular septum. The main clinical sign—appearance of a loud systolic murmur in the course of recent myocardial infarction—may be obscured if the patient is seen some time after the perforation. The diagnosis may be suggested by the electrocardiogram, the suggestive findings being right heart strain in the absence of cor pulmonale and/or the pattern of posterior wall infarction in the limb leads, and anterior wall infarction in the chest leads.

PICK

PHYSIOLOGY

Knutson, J. R. B., Taylor, B. E., Ellis, E. J., and Wood, E. H.: Studies on Circulation Time with the Aid of the Oximeter. Proc. Staff Meet. Mayo Clin. **25:** 405 (July), 1950.

While previous studies with the oximeter have been concerned primarily with the determination of oxygen saturation of the blood, the instrument is adaptable to the study of other circulatory variables. Circulation time from the lung to the ear can be determined by suddenly changing the oxygen content of the gas mixture being breathed and measuring the elapsed time to the onset of the resultant change in the oxygen saturation of the blood at the ear. In this instance, the elapsed time required is a measure of the time required for the production of a change in the oxygen tension in the alveoli, the consequent change in oxygen tension in the pulmonary capillaries, and the time required for the blood to flow from the pulmonary capillaries to the left side of the heart and out into the systemic circulation to the ear. This so-called lung-to-ear circulation time can, therefore, be affected by several factors unrelated to the actual circulation time from the lungs to the ear. The use of the whole-blood cuvette oximeter attached to an indwelling needle in an artery or vein, or to an indwelling arterial or venous catheter, makes possible the measurement of the "circulation time" to other portions of the body.

The oximeter can also be used to measure the time required for circulation of injected dyes which possess spectral absorption characteristics. Methylene blue and Evans blue (T-1824) are two such dyes. The contours and magnitudes of dye injection curves may provide more objective diagnostic evidence than does the time sequence of the tracing.

The arm-to-lung time determined by the ether injection method in 10 normal subjects was not significantly different from that calculated by subtracting the lung-to-ear from the arm-to-ear time determined by the oximeter.

SIMON

Wood, E. H.: A Single Scale Absolute Reading Ear Oximeter. Proc. Staff Meet. Mayo Clin. **25:** 384 (July), 1950.

A simplified version of the single scale oximeter has been designed which is completely operated on 110 volt A.C., and in which the switching and control circuits are incorporated as an integral part of a standard box-type portable galvanometer. If the calibration settings of the earpiece are known, the technic for operation can be mastered easily. With this instrument an operator can readily complete an initial estimate of the percentage saturation of arterial blood with oxygen in a five minute period, and a practically continuous record of the arterial oxygen saturation of the subject can be obtained for any desired period thereafter.

Extensive calibration data of an earpiece and a cuvette against direct manometric analyses of blood indicate that in oxygen saturation above 90 per cent the variability of the single scale method of operation is similar to that of the double scale method of operation and compares very favorably with that of Van Slyke analyses of arterial blood. The variability of the single scale method of operation, however, increases considerably more in the lower ranges of saturation than does that obtained with double scale operation. This greater variability in the low ranges of saturation is partially compensated by the multiple chances for galvanometer reading and calculation errors unwittingly introduced when the double scale method is used.

SIMON

Crehan, E. L., Kennedy, R. L. J., and Wood, E. H.: A Study of the Oxygen Saturation of Arterial Blood of Normal Newborn Infants by Means of a Modified Photo-electric Oximeter: Preliminary Report. Proc. Staff Meet. Mayo Clin. **25:** 392 (July), 1950.

Studies were conducted on 81 infants varying in age from 3 hours to 7 days. These subjects were divided into 8 groups according to age. The average saturation of arterial blood of the various age groups during the first week of life fell within the range of individual values found in normal adult persons. Single determinations, however, frequently fell below this range. The results tend to show that under the

conditions of these studies normal newborn infants, although very hypoxemic at birth, have a rapid increase in the oxygen saturation of arterial blood so that at 17 minutes of age the average value falls within the range of individual values obtained for normal adults. The studies carried out during the first 7 days after birth indicated that transient decreases in saturation to values below the range obtained for normal adults occurred frequently, especially when these infants were sleeping or resting quietly. Spontaneous recovery of the saturation of arterial blood to the normal range regularly occurred when the infant was awakened or startled. That these transient decreases in arterial saturation were probably pulmonary in origin and that the infant oximetric values were reasonably accurate is indicated by the fact that the arterial saturation readings uniformly increased to values not significantly different from 100 per cent when the infants were exposed to an atmosphere containing 90 per cent oxygen.

SIMON

Polzer, K., and Schufried, F.: Rheocardiography of the Chest Wall. Cardiologia **16:** 1, 1950.

The authors describe a method (rheocardiography) of registering periodic changes of conductivity within the human body during the cardiac cycle. Two electrodes, one on the right shoulder and the other over the heart of the patient, are connected with one arm of a Wheatstone bridge. Variations in voltage occurring in the system are amplified and registered by an electrocardiograph. In the curves obtained by this method, different parts of the heart cycle can be determined. The authors present examples of abnormal tracings, which in their opinion are characteristic for disturbances in hemodynamics of valvular lesions and heart failure. Certain conclusions can also be drawn concerning the dynamics of the peripheral circulation.

PICK

RHEUMATIC FEVER

Denny, F. W., Wannamaker, L. W., Brink, W. R., Rammelkamp, C. H., Jr., and Custer, E. A.: Prevention of Rheumatic Fever. Treatment of the Preceding Streptococcic Infection. J.A.M.A. **143:** 151 (May), 1950.

The prevention of acute rheumatic fever by the prompt treatment of streptococcic infections with penicillin was attempted in this study. Only patients having exudate on the tonsils or on the pharyngeal wall, a total of 1,634, were included in the study group. A total of 798 patients, whose serial numbers ended in an even digit, received penicillin treatment, and 804 patients, whose serial numbers ended with an odd digit, received no specific treatment and were used as controls. Of the specifically treated patients, 253 received 300,000 units of crystalline procaine penicillin G (suspended in peanut oil containing 2 per cent aluminum monostearate) intramuscularly as soon after admission as possible, and the dose was repeated in 72 hours; 545 of the specifically treated cases received 300,000 units of the same preparation at the time of admission and again in 48 hours, and 600,000 units were received 96 hours after the initial dose. The authors performed follow-up studies for the detection of rheumatic fever between the third and fourth weeks after the initial infection, using rigid criteria based upon a modification of the classification of T. Duckett Jones. Of the 798 treated patients 2 developed definite acute rheumatic fever; 17 of the controls were found to have this disease. This difference between the two groups could be due to chance only 6 times in 10,000. Probable acute rheumatic fever developed in 2 patients in the treated group and in 6 patients in the untreated group. It is felt that this evidence is sufficient to indicate that rheumatic fever can be prevented by the treatment of streptococcic disease with penicillin.

KITCHELL

Loutfy, K. D., and Cairo, M. B.: Rheumatic Aortic Aneurysm in a Boy of 19. Lancet **1:** 996 (May), 1950.

Loutfy reports a case of aortic aneurysm occurring in a youth of 19 whose past history and clinical findings left no doubt as to a rheumatic etiology. He discusses the rarity of this condition and reviews the literature. The case reviewed showed, in addition to the major features of aortic aneurysm, the presence of severe rheumatic heart disease involving the mitral and aortic valves. His serologic studies were negative for syphilis, blood cultures were repeatedly negative, and there was no suggestion of dilatation above a coarctation of the aorta.

TANDOWSKY

ROENTGENOLOGY

Muller, W. H., Jr., and Sloan, R. H.: Experiences with the Use of Direct Aortography in the Diagnosis of Coarctation of the Aorta. J. Thoracic Surg. **20:** 136 (July), 1950.

A method for direct aortography is described for visualization of the area of coarctation. This method utilizes the left radial artery and permits a catheter to enter the descending aorta. With local anesthesia the radial artery is exposed in the antecubital fossa. Its nearest large tributary is isolated, a ligature placed on it distally, and a small bulldog arterial clamp proximally. A small transverse incision is made in the occluded portion and a size 9 or 10 intravenous catheter introduced into it. The clamp is removed and the catheter passed into the subclavian artery to the mediastinum or to the coarctation itself. The catheter is then withdrawn 1 to 2 cm. The procedure is performed on a fluoroscopic table and the exact site of the catheter tip observed. Twenty-five cc. of 70 per cent Diodrast is then injected rapidly and films are taken at one second intervals by means of an automatic cassette changer.

A total of not more than 75 cc. is given during the procedure. The catheter is withdrawn after a ligature is placed about the tributary.

Thirteen cases were subjected to this procedure. Nine cases showed the usual type of coarctation at operation. In 1 case a patent ductus was found in addition to the coarctation. In another an aneurysm of the first left intercostal artery was visualized. A third case had aneurysm of both first intercostals which were not visualized on the aortogram. A fourth case had a dissecting aneurysm of the aorta immediately distal to the coarctation not demonstrated on the aortogram.

This method assures visualization of the ascending aorta and eliminates the possibility of the catheter's obstructing the orifice of one of the coronary arteries. A smaller amount of contrast substance is required, and the greatest amount of contrast substance is placed at the site of the coarctation.

KLOSK

SURGERY IN HEART AND VASCULAR SYSTEM

Brunner, W.: The Surgical Treatment of Arterial Hypertension. Schweiz. med. Wchnschr. **80:** 541 (May), 1950.

Surgical treatment can completely cure arterial hypertension, if the latter is due to coarctation of the aorta, to a solitary tumor of the adrenal medulla or to unilateral kidney disease. Sympathectomy represents an attempt to decrease, by surgical methods, the peripheral vascular resistance, which, however, depends not only on sympathotonic factors, but also on endocrine and humoral factors. Sympathectomy is indicated primarily in patients below the age of 40 years. At this age, the author observed improvement of symptoms even in cases of malignant hypertension which were followed for a period of one year after the operation. Contraindications are arteriosclerosis, repeated cerebral accidents, mental disturbances, heart failure not responding to treatment, auricular flutter and fibrillation heart block and angina pectoris. An immediate improvement following operation (disappearance of headache and of retinopathy) can be ascribed to an orthostatic fall of tension. The persistence of subjective improvement despite rising blood pressure is probably due to an altered distribution of the blood within the body. In his 30 cases of hypertension, in which sympathectomy was performed the author had no operative fatality.

PICK

Baronofsky, I. D., and Skinner, A.: Ligation of Left Auricular Appendage for Recurrent Embolization. Surgery **27:** 848 (June), 1950.

Three cases of rheumatic heart disease with mitral stenosis and recurrent embolization are reported, in which further embolic phenomena were prevented by ligation of the left auricular appendage at its base. The course of each patient during the surgical procedure and in the immediate postoperative convalescent period was uneventful. The authors chose this procedure because of its simplicity and safety as compared with resection of the auricular appendage. No effort was made in these cases to remove the thrombus, although it was suggested that in future cases the tip of the appendage be opened and the thrombus removed. This latter procedure should be done, however, only after preliminary ligation of the base of the appendage.

KLOSK

Lohom, A. J., and Shrock, J. B.: Pheochromocytoma with Persistent Hypertension and Thoracolumbar Sympathectomy. Surgery **27:** 935 (June), 1950.

A case of sustained arterial hypertension treated by sympathectomy is reported, in which subsequent autopsy showed the presence of an undiagnosed pheochromocytoma. Following lumbodorsal sympathectomy, the patient no longer had persistent hypertension, but had wide swings of blood pressure with symptoms of postural hypotension and attacks of hypertension due to excessive adrenaline secretion. The authors stress the importance of careful palpation of the adrenal glands during lumbodorsal sympathectomy in order to rule out pheochromocytoma.

KLOSK

McKhann, C. F., Belnap, W. D., Beck, C. S.: Cervical Arteriovenous Anastomosis in Treatment of Mental Retardation, Convulsive Disorders and Cerebral Spasticity. Ann. Surg. **132:** 162 (Aug.), 1950.

An attempt was made to increase the cerebral blood supply in 125 patients with localized or generalized gliosis of the brain by producing a fistula between the carotid artery and the internal jugular vein. The latter was tied off and cut proximal to the anastomosis to prevent blood from returning directly to the right side of the heart. It was felt that blood under arterial pressure in the venous system would thus be freely distributed throughout the capillary anastomosis of the cortex.

In 39 children with mental retardation secondary to various types of organic brain injury, definite signs of improvement followed operation in the majority of cases. In 35 per cent these were objective while in 19 they were subjective. The remainder failed to show improvement. In 34 cases of convulsive disorders, 5 had complete absence of attacks postoperatively, 9 showed complete control, and 6, improvement with added medication. Most of these had previously been refractory to anticonvulsant therapy.

The procedure, in the early stage of evaluation, should be considered a new approach to the problem rather than an acceptable and complete solution.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Farmer, D. A., and Smithwick, R. H.: Thromboembolic Disease. A Discussion of the Problem in Surgical Patients with Particular Reference to the Fatal Embolus. Angiology **1:** 291 (Aug.), 1950.

Ninty five cases of thromboembolic disease occurred among 7343 consecutive general surgical admissions. The importance of prophylaxis is emphasized by the fact that pulmonary infarction was the first sign in 25 per cent of the 95 cases and was fatal in 38 per cent of the cases in which it occurred. To identify those patients who would be most likely to develop thromboembolic disease, the authors established an arbitrary scoring system utilizing 15 predisposing factors graded from 1 to 3. It is concluded that any patient with a score of 6 or higher should be seriously considered for some form of prophylactic therapy.

WESSLER

Sullivan, J. M., and Walske, B. R.: Thrombophlebitis Migrans. Ann. Surg. **132:** 260 (Aug.), 1950.

The authors report a case of thrombophlebitis migrans in a 25 year old male who had numerous attacks of superficial and deep thrombophlebitis of both legs and of the abdominal wall. In the last admission abdominal distension occurred; two abdominal explorations were performed. Chronic adhesive peritonitis was found at operation. The patient went into shock following the second operation and died. At autopsy multiple thromboses of mesenteric, splenic and portal veins were observed, associated with infarction of jejunum and ileum.

The etiology of thrombophlebitis migrans remains obscure. It is a disease of the young and middle aged, and is about four times as common in males as in females. In the differential diagnosis the phlebitis of Buerger's disease must be ruled out. The superficial veins of the extremities and, to a lesser degree, of the abdomen and thorax are most frequently involved. Other parts of the body may also be affected. The segment of vein affected is usually small, it gives rise to tenderness and redness, and the process subsides in a matter of days or weeks. Fever and leukocytosis commonly accompany each attack, and involvement of visceral veins is the most serious complication.

There is no specific therapeutic agent for the condition, although the anticoagulants appear to be beneficial in limiting the duration and extent of each recurrence. Ligation is not ordinarily recommended because emboli, when they occur, are small. Furthermore, such a procedure is not practicable, since recurrences appear in widely disseminated areas.

ABRAMSON

Bourne, G.: Embolism in Mitral Stenosis. Brit. Heart J. **12:** 263 (July), 1950.

The relationship between exercise and embolism in mitral stenosis was studied in 29 individuals who had 31 embolic accidents. Twenty-three showed auricular fibrillation and 6 had regular rhythm. Twenty-four had good exercise tolerance. Only 3 had congestive failure. Only 2 embolic accidents occurred while the individuals were actively mobile. Seven with auricular fibrillation suffered embolic accidents while undertaking easy physical exercise, 13 while sitting and 9 while asleep in bed. The author concludes that embolism is not directly related to physical effort, is not usually due to clot formation in the dilated auricle of severe congestive failure, and is most common in those with good exercise tolerance in whom the mitral orifice is fairly large.

SOLOFF

VASCULAR DISEASE

Valdes-Dapena, A. M., Valdes-Dapena, M. A., and Pocock, D. S.: Renal Vascular Lesions in Diabetes. J. Philadelphia General Hosp. **1:** 8 (April), 1950.

Renal lesions were studied in 429 known autopsied diabetic patients. In addition 100 kidney sections from uremic patients who were nondiabetics, and 50 kidney sections of benign and malignant hypertensives were reviewed. Sixty per cent of all diabetics showed some degree of glomerular sclerosis, ranging from the early diffuse type to the obvious hyaline sphere lesion. Twenty-four per cent showed frank glomerular sclerosis. Arteriolosclerosis was frequently encountered and was present in a marked degree in 25 per cent of the cases. It paralleled the severity of glomerular involvement. Massive albuminuria and edema were the most constant clinical accompaniment of the severe stages of this process. A significant drop in serum albumin was a connecting link between albuminuria and edema.

Hypertension was found somewhat more frequently in patients presenting this lesion than in other diabetics. Renal insufficiency or azotemia was no more frequent in the presence of this lesion than in other diabetics. Similar lesions were not found in nondiabetic hypertensive and uremic patients.

WAIFE

Silberman, D. E., Rowntree, L. G., and Orenstein, H. B.: Recovery from Addison's Disease Due to Diffuse Vascular Disease with Subsequent Development of Hypertension and Glomerulonephritis. Ann. Int. Med. **32:** 760 (April), 1950.

In the reported patient the characteristic picture of Addison's disease developed at the age of 20. The etiology was considered to be atrophy of the adrenal glands on a vascular basis. The addisonian symptoms, except for the pigmentation, were largely improved by hormonal therapy and administration

of suitable electrolytes. At the age of 24, he developed convulsions and temporary psychotic episodes which were found to be due to spontaneous hypoglycemia. By appropriate treatment of the hypoglycemic syndrome, these symptoms disappeared. When he was 25 years of age, a biopsy of skin and muscle from the left deltoid region showed fibrinoid degeneration and necrosis within arteries and arterioles with variable degrees of vascular occlusion and increased melanin in the stratum germinativum of the skin. At the age of 28, he developed retinal hemorrhages and systolic and diastolic hypertension and abnormal urinary findings. From then on, he gradually deteriorated, became more stuporous and died while in a comatose state. On the basis of the gross and microscopic findings of the necropsy material, the following diagnoses were made: Generalized obliterative angiitis; subacute and chronic glomerulonephritis; extensive fibrosis with marked cortical regeneration of the suprarenal glands and absence of the adrenal medulla (probable old infarction); multiple regions of softening of the brain; pigmentation of the lips, external genitalia, skin, nipples and buccal mucosa; atrophy and fibrosis of the thyroid with marked lymphocytic infiltration and adenoma formation; subinvolution of the thymus; hypertrophy and dilatation of the left ventricle; patchy myocardial fibrosis of the left ventricle; atherosclerotic coronary artery disease with thrombotic occlusion of the right coronary artery; organizing nonbacterial thrombotic endocarditis of the mitral valve; multiple old and recent infarcts of the spleen; chronic splenitis with splenomegaly; acute and chronic pneumonitis. This case is unusual in that a generalized obliterative angiitis with involvement of the adrenal vasculature was responsible for the Addison's disease.

WENDKOS

Fraenkel, G. J., and Neil, J. F.: Dissecting Aortic Aneurysm Simulating Arterial Embolism. Lancet **1:** 801 (April), 1950.

The authors discuss the misleading symptoms of dissecting aortic aneurysm which not infrequently lead to the diagnosis of peripheral vascular disease. Two cases are presented. In one the antemortem diagnosis of embolism of the right femoral artery was made, while in the other it was felt than an embolism had occurred in the right arm, probably from an aortic plaque. The differential diagnosis between dissecting aortic aneurysm and embolism is discussed and the treatment of dissecting aneurysm and peripheral embolism are briefly reviewed.

TANDOWSKY

Hejtmancik, M. R., Bradfield, J. Y., and Rigdon, R. H.: Pulmonary Arteritis Due to Acquired Syphilis. Am. J. Syph., Gonor., & Ven. Dis. **34:** 236 (May), 1950.

The authors report a case of syphilitic involvement of the aortic arch and pulmonary artery, with possible spread to the adjacent lung tissue and smaller pulmonary arteries. The patient was a 56 year old woman admitted to the hospital because of paroxysmal nocturnal dyspnea and dependent edema. The blood serologic tests had been positive for the previous seven years, and the patient had received sporadic antisyphilitic therapy. Examination of the lungs revealed moist rales posteriorly. The heart was enlarged and aortic insufficiency was present. With cardiac management the patient was able to leave the hospital in a compensated state but returned three months later with symptoms of recurrence of heart failure. Despite treatment, the patient developed a shocklike state and died. Autopsy revealed a syphilitic process around the orifices of the vessels leaving the aortic arch and thrombosis of the left branch of the pulmonary artery. Histologically the walls of the arteries in the left lung were very thick and the lumina were partially occluded by an endarteritic process. The diagnosis was syphilitic pulmonary arteritis with a mural thrombus. It was suggested that the spirochetal infection might have extended from the aorta to the pulmonary artery, inducing the productive cicatricial type of lesion.

ABRAMSON

Popkin, R. J.: A Systolic Murmur Heard over the Lower Abdominal Aorta: Its Significance in Peripheral Vascular Diseases. Angiology **1:** 244 (June), 1950.

In a consecutive series of 35 patients with either arteriosclerosis obliterans or thromboangiitis obliterans, a systolic murmur over the abdomen was elicited by auscultation in 22 cases. In a similar group of 35 patients without peripheral vascular disease, the murmur was not heard. It is stated that the murmur arises from the lower abdominal aorta; its mode of production is not known.

WESSLER

Paterson, J. C., and Cottral, G. E.: Lymphomatosis as a Cause of Coronary Sclerosis in Chickens. Arch. Path. **49:** 699 (June), 1950.

The writers point out that coronary sclerosis is common in adult fowl, occurring as a focal cellular infiltration and hydropic degeneration in the media. Cholesterol is not an etiologic factor; however, its ingestion in large amounts increases the size of the plaques and adds to their lipoid content. An extremely common neoplastic disease of chickens is lymphomatosis. The writers suspected that it is an etiologic factor in the development of coronary sclerosis. They observed two groups of chicks, one a control, the other subjected to intratracheal instillation of pooled tracheal washings from adult birds suffering from advanced lymphomatosis. At the end of one year, autopsy revealed a sixfold increase of

coronary arteriosclerosis in the infected birds. The medial lesions and the overlying intimal lipoid thickenings were strikingly increased in number and size.

"Spontaneous" coronary arteriosclerosis in chickens is possibly the vascular type of lymphomatosis. The latter exists as an avian disease in many forms, none of which have been transmitted to man. The authors, however, believe the mechanism of development of arteriosclerosis in the two species may be similar.

GOULEY

OTHER SUBJECTS

Lochner, W., and Schoedel, W.: The Blood Volume of the Lesser Circulation and the Minute Volume of the Heart. Pflüger's Arch. f. d. ges. Physiol. **252:** 281 (March), 1950.

The authors describe a method for simultaneous determination of pulmonary flow and cardiac output. In anesthetized dogs, the pulmonary flow was found to increase if the cardiac output rose following arterificial arteriovenous fistulas or transfusions. A fall in pulmonary flow occurred following venesection or cooling of vagi and sympathicus. The latter procedure, however, produced an increase of cardiac output. The observation that alterations in pulmonary flow do not produce, but follow changes of cardiac output contradicts the assumption that the pulmonary vascular field acts as a blood depot for the systemic circulation.

PICK

Motokawa, K., and Iwama, K.: The Electric Excitability of the Human Eye as a Sensitive Indicator of Oxygen Deficiency. Tohoku J. Exper. Med. **50:** 319 (June), 1949.

The authors point out that the electric excitability of the human eye is a sensitive measure of oxygen deficiency. A sensation of flickering light can be produced by stimulating the eyes with alternating electric current of various frequencies. The authors were able to achieve a similar effect by using a periodically interrupted direct current instead of an alternating current. Experiments were conducted in a low pressure chamber. Using electrodes applied to the forehead and occiput, the voltage of the stimulating current was gradually increased up to 14 volts until the subject noted a flicker sensation synchronous with the pulsation of the electric current at a particular voltage level. In addition to the threshold for the appearance of the flicker sensation (Va), the threshold for the disappearance of the flicker (Vd) was measured when the voltage was gradually decreased from its Va value. It was found that the Vd value was very slightly lower than the Va level. When the atmospheric pressure in the test chamber was lowered to a point equivalent to an altitude of 9,830 feet, there was a rise in Va and a lowering of Vd although the mean value of Va and Vd remained unaltered. When a subject using an oxygen mask was exposed to a pressure equivalent to an altitude of 22,950 feet, the value for Va remained normal, but when the oxygen mask was removed there was an immediate rise in the Va level to over twice the normal level.

Comparison of the electric excitability of the eye with the determination of sensitivity of the eye to light revealed that the former method is more suitable for clinical measurement of oxygen deficiency because of its accuracy, rapidity, and ease of application.

SCHWARTZ

Hinkle, L. E., Jr., Conger, G. B., and Wolf, S.: Studies on Diabetes Mellitus: The Relation of Stressful Life Situations to the Concentration of Ketone Bodies in the Blood of Diabetic and Non-Diabetic Humans. J. Clin. Investigation **29:** 754 (June), 1950.

Stressful situations may produce a rise in venous blood ketones in both diabetic and nondiabetic humans. Ketonemia was much greater in the diabetic. With relative emotional security, the blood ketone levels returned to normal levels without extra insulin. Blood sugar changes were variable. The authors suggest that the mechanisms involved may include disturbances of the anterior pituitary and adrenal glands.

WAIFE

Borden, C. W., Wilson, R. H., Ebert, R. V., and Wells, H. S.: Pulmonary Hypertension in Chronic Pulmonary Emphysema. Am. J. Med. **8:** 701 (June), 1950.

In 24 patients with chronic pulmonary emphysema, cardiac catheterization revealed a significant elevation of the pulmonary arterial diastolic pressure (mean pulmonary diastolic pressure 22 $\pm$ 7 mm. Hg) related to increased vascular resistance in the lungs. In a majority of the patients, the pulmonary systolic pressure was elevated. There was no correlation between the degree of pulmonary hypertension and the severity of the emphysema as estimated by the altered ratio of residual air to total lung volume. The pulmonary arterial pressure was significantly higher and the oxygen saturation of the arterial blood lower in 8 patients with previous history of right heart failure than in 16 patients without this history. The mean arteriovenous oxygen difference in 23 patients with pulmonary emphysema was similar to that reported in normal subjects. There was no evidence that oxygen unsaturation of the arterial blood in pulmonary emphysema induces an increase in the cardiac output.

HARRIS

Brinton, W. D.: Primary Pulmonary Hypertension. Brit. Heart J. **12:** 305 (July), 1950.

The author reports an instance of primary pul-

monary hypertension in a man 26 years of age; necropsy showed atheroma and mural thrombosis of the main branches of the pulmonary artery and internal thickening with obliteration of the lumen of 2 small bronchial arteries in the periphery of the lung. In the region of the right hilum were two conglomerations of communicating arteries and veins forming complicated arteriovenous aneurysms. They appeared to arise from bronchial and pulmonary arteries and veins. It is suggested that primary pulmonary hypertension results from excessive entry of blood into the lesser circulation from the bronchial arteries. The increased pressure causes dilatation and sclerotic changes in the pulmonary artery and hypertrophy with eventual failure of the right ventricle.

SOLOFF

Hyde, T. L., Moore, L. V.: Resuscitation after Apparent Death from Spinal Anesthesia. J. A. M. A. **143:** 805 (July), 1950.

A 26 year old woman, in excellent health except for gallstones, was anesthetized with piperocaine hydrochloride (metycaine hydrochloride), and cholecystectomy was begun. Twenty-five minutes later pulse and respiration ceased, and the patient apparently died. The left hand of the surgeon was introduced into the abdomen, and the heart was massaged through the diaphragm by being squeezed between the palmar surface of the hand and the anterior chest wall. It was noted that upward pressure of the massaging hand on the heart would produce respiratory exchange. It was also found that, while continuing the rapid massage of the heart performed by the left hand inside the abdomen, adequate respiration could be produced by slow alternate lifting and depressing of the lower end of the sternum with the right hand (the fingers being hooked around the sternal manubrium). Twelve minutes after the anesthetist had announced the cessation of pulse, rapid regular heart beats began. Artificial respiration still had to be maintained for 32 minutes. The authors conclude that such massage of the heart can adequately maintain circulation for 12 minutes or longer, and that manipulative artificial respiration by rhythmic alternate upward and downward pressure on the lower end of the sternum is effective and easily done.

KITCHELL

Evans, E.: Acute Nonspecific Benign Pericarditis. J.A.M.A. **143:** 954 (July), 1950.

The author presents 11 cases of acute benign nonspecific pericarditis seen in private practice in a subtropical climate. He draws attention to the fact that all the patients had chest pain aggravated by body motion or deep inspiration which helped to differentiate the condition from acute myocardial infarction. The pericardial friction rub is heard early in this disease rather than three or four days after the onset as is commonly noted in infarction. Mild fever was present and was associated with increased sedimentation rate and leukocytosis in most cases. Eight of the patients were given penicillin; however, the effect of this is dubious because the disease itself is self-limited. Electrocardiographic changes indicative of pericarditis were noted in 10 cases. Two of the cases reported were associated with chronic rheumatic valvular heart disease.

KITCHELL

Keys, A., Mickelson, O., Miller, E., and Chapman, C. B.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood. Science **112:** 79 (July), 1950.

The authors show that with a rigorous cholesterol-free diet the blood cholesterol may be readily and rapidly lowered both in normal men and in men with extreme hypercholesterolemia. However, the blood cholesterol level is independent of the intake over a wide range, and most of the so-called low cholesterol diets in current use are probably ineffectual.

SACHS

Gelfan, S., Nims, L. F., and Livingston, R. B.: Explosive Decompression at High Altitude. Am. J. Physiol. **162:** 37 (July), 1950.

Survival time for rats decompressed rapidly to altitudes above 52,000 feet is twice as long in 100 per cent oxygen as it is in air. The maximal survival time above this altitude is fixed at approximately 40.0 seconds in oxygen, and 18.0 seconds in air. At altitudes below 52,000 feet, survival time in oxygen progressively increases, and at a much more rapid rate than in air.

Similarly, survival by recompression from high altitudes at free-falling rate is markedly enhanced in 100 per cent oxygen. From an altitude of 65,000 feet 87 per cent of a group of rats survived in pure oxygen compared with a mortality of 100 per cent in air.

Examination of the lungs of rats surviving rapid decompression and recompression at free-falling rates in both 100 per cent oxygen and air revealed a marked capacity for recovery of injury sustained. The most frequent changes, emphysema, edema, and cellular infiltration, were only minimal 24 hours after conclusion of the experiment. Hemorrhage in the middle ear was observed in 37 per cent of rats exposed to altitudes above 45,000 feet.

HECHT

Keys, A., Mickelsen, O., Miller, E. O., and Chapman, C. B.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood. Science **112:** 79 (July 21), 1950.

An analysis was made of the effect of long term alterations in the cholesterol content of the diet on 482 clinically normal men. With ranges in habit-

ual cholesterol intake of 250 to 800 mg. a day, no significant differences in serum levels were found. Forty-one middle aged normal males were studied before and after a 50 per cent reduction of cholesterol intake. One year later, and after at least several months of low cholesterol intake, the mean cholesterol level was unchanged. Four patients were maintained on the rice-fruit diet which is cholesterol-free. The mean total cholesterol value fell from 232 mg. per 100 cc. of serum to 151 mg. after about three weeks. The rate of fall was related to the previous level of cholesterol.

The authors doubt whether most so-called low cholesterol diets reach critical levels or are significant in reducing serum levels. One patient when changed from a cholesterol- and fat-free diet to one containing vegetable fats, but without cholesterol, had a return of serum level almost as rapid as it had fallen. This confirms other reports that vegetable oils in the diet promote cholesterol accumulation in the body even on a cholesterol-free diet.

WAIFE

Comroe, J. H., Jr., Bahnson, E. R., and Coates, E. O., Jr.: Mental Changes Occurring in Chronically Anoxemic Patients during Oxygen Therapy. J. A. M. A. **143:** 1044 (July), 1950.

Because of the occasional report of an undesirable reaction following the administration of oxygen to patients with chronic anoxemia, the authors studied the development of mental changes, ranging from somnolence to coma, in 8 of 65 patients with mild to severe chronic anoxemia, who were given high concentrations of oxygen to breathe. The possible mechanisms for the causation of such pictures are discussed. They include carbon dioxide narcosis, cerebral vasospasm, reflex depression of cerebral cortex by high oxygen tension, increased cerebrospinal fluid pressure, and direct depression of the cerebral cortex by high oxygen tension. The authors agree with Barach that in chronic anoxemia coma may be prevented if a low concentration of oxygen is used to begin therapy.

KITCHELL

Callebaut, C., Lequime, J., and Denolin, H.: The Oxymetric Method for Determining Circulation Time in Man. Acta cardiol. **5:** 137, 1950.

The oxymetric method enables us to determine precisely the circulation time, arm to ear (by injection of methylene blue), and lung to ear (by inspiration of nitrogen). In a normal case, the arm to ear time is 10.3 seconds, and the lung to ear time is 5.12 seconds on the average. Repeated measurements on the same case give identical results. Such technics eliminate the reacting time which is unavoidable with the taste methods and the ether method. They enable us to divide the complete circulation time in different circuits. This data has numerous clinical and experimental applications.

AUTHORS

Maxwell, M. H., Breed, E. S., and Smith, H. W.: Significance of the Renal Juxtamedullary Circulation in Man. Am. J. Med. **9:** 216 (Aug.), 1950.

Maxwell and associates examined the by-pass role of the juxtamedullary glomeruli and from both morphologic and physiologic considerations conclude that, whatever its significance in the rabbit, the juxtamedullary circulation has no specific functional significance in man as far as can now be ascertained. Experimental perfusion of the juxtamedullary circuit during cortical ischemia has been partially confined in the rabbit, but has failed of confirmation in the dog, as in man. This circumstance may reflect a species difference in the fetal development of the kidney and the degree of renal maturity at birth.

HARRIS

Scholer, H., and Springenschmid, M.: Remarks on Phonocardiography. Schweiz. med. Wchnschr. **80:** 807 (Aug.), 1950.

Following a discussion of the physics of phonocardiography the authors present and illustrate their experiences with a new Swedish instrument (Elema Type EM 130), a multibeam phonocardiograph, which permits the synchronous registration of acoustic phenomena of the heart at various filtered frequencies. By synchronization with an electrocardiogram, the onset of heart sounds can be timed exactly, permitting a more accurate determination of the mechanical systole. Duration and various qualities of heart sounds and heart murmurs can be demonstrated and different types of additional (gallop) sounds can be distinguished by more accurate timing within the cardiac cycle. The time of isometric contraction and ejection of the ventricles can be determined by pairing a phonocardiogram with a rheocardiogram.

PICK

BOOK REVIEWS

Le rétrécissement mitral. Etudes anatomiques, cliniques et thérapeutiques. *R. Lutembacher.* Masson et Cie, Paris, France, 1950. 304 pages, 123 figures, 1400 francs.

This monograph on the subject of mitral stenosis and associated conditions is written by one of the best known of contemporary French cardiologists. It contains an immense amount of detailed discussion of the pathologic variations, physical diagnosis, clinical course and methods of treatment of mitral disease, supplemented by 82 case reports. It reflects largely the author's great personal experience but includes numerous references to the published work and opinions of others.

Dr. Lutembacher has written what is, in many respects, an excellent treatise. To the reviewer however, it seemed unnecessarily lengthy due to predominant emphasis on certain topics such as pathology and clinical diagnosis, with considerably less attention to others. In addition, the section on treatment tends to arouse some skepticism. The author believes for example, that the inadequacy of salicylate therapy in rheumatic fever is due to failure to give salicylates intravenously rather than by mouth. He advises the intravenous administration of ouabain for routine digitalization. Intravenous Convallatonine is said to promptly reduce the size of a congested liver when digitalis fails to do so. Intravenous injections of tyramine and of glucose and insulin are prescribed routinely for congestive failure. Intravenous iodides are recommended for mitral stenosis at any stage of the disease. One gains the impression, in fact, that medication should almost never be given by mouth if any other route of administration is available. The only statement regarding the use of oral digitalis is a comment that in some cases, after intravenous ouabain has been taken for a time, 15 to 21 drops of digitalin may be given daily for two or three days and repeated every seven to fifteen days. As for the mercurial diuretics, they are mentioned only once, as helpful in the management of a complicating menstrual syndrome.

In spite of certain shortcomings suggested above, this book can scarcely be read without finding many interesting and previously unfamiliar facts and opinions. The references, mostly French and a large proportion of them historic rather than contemporary, are also a valuable feature although unfortunately only the authors' names are cited, mention of the publications being omitted.

L. B. LAPLACE

You and Your Heart. *H. M. Marvin, Irving S. Wright, Irvine H. Page, T. Duckett Jones* and *David D. Rutstein.* New York, Random House, 1950. 306 pages, $3.00.

The lay public now has available an authoritative review of the main aspects of cardiovascular disease. The major problems concerning the circulation are taken up by experts in this field. First, there is a general discussion of the normal heart and circulation. Then there follows a survey of the important types of diseases of the heart and blood vessels. There are chapters on congenital heart disease, coronary disease, rheumatic fever and rheumatic valvular disease, hypertension, diseases of the peripheral arteries and veins and finally on the public health aspects of heart disease. Each subject is covered by men who are outstanding authorities in their respective fields.

Although this book is primarily intended for the nonmedical public, it contains much useful information for the general practitioner, particularly emphasizing the preventive measures that are available. It presents the immense problem of heart disease in a simple truthful fashion. It does not strike terror in the mind of the reader, but rather gives him intelligent hopefulness and support. It will help to dispel many false and harmful superstitions, errors that are still too prevalent even amongst intelligent people. Physicians will find it useful to encourage their patients to read such a book, as it can help in a better cooperation in the follow-up care of those with cardiac disease. At last we have a volume that can readily be recommended to the public. It does not raise false hope nor does it make the reader despair.

S. A. LEVINE

Diseases of the Aorta. Diagnosis and Treatment. *Nathaniel E. Reich.* New York, Macmillan Company, 1949. 288 pages, 60 figures, $7.50.

This monograph brings within one volume a consideration of the many abnormalities and pathologic lesions of the aorta by an author who has long had a special interest in this main arterial pathway. Most treatises on cardiovascular disease stress the cardiac conditions or the peripheral vascular problems and give little attention to the intervening aorta. This new volume fills the gap and focuses attention upon this largest of arteries.

Anatomic, histologic and pathologic descriptions are given in a brief style. Congenital defects, until recently thought impossible to correct, are described and the forms of surgical therapy are indicated. The newest advances in diagnosis and treatment of

syphilis, arteriosclerosis, occlusions, dissecting aneurysms, and rare diseases involving the aorta are reviewed in a clear manner. Diagnostic procedures, with and without the use of x-ray technics, are outlined and particular emphasis is placed upon the fact that many aortic lesions can be recognized by simple means which are inexpensive and are available to all practicing physicians. A wide study of the literature has yielded an extensive bibliography which has been carefully condensed so that the reader has before him only the more pertinent and helpful references.

The book is adequately illustrated with sketches and halftone illustrations. The text has an easily readable and attractive style. The various chapters are not swamped with unimportant and rare details which so many authors of monographs feel obliged to include for the sake of completeness. This new book gives in a concise way the most important features of the many conditions which can appear in the aorta and which are receiving increasing attention by the medical and surgical profession.

ROBERT E. GROSS

Management of Peripheral Arterial Diseases. *Samuel S. Samuels.* New York, Oxford University Press, 1950. 345 pages, 112 illustrations, $7.50.

The author has performed an important service in emphasizing certain aspects of the management of gangrene which are ordinarily neglected. With the present day interest in vasodilator drugs and procedures, the local treatment of gangrenous tissue all too frequently is inadequately and improperly carried out. Very often the manner in which necrotic tissue in an ischemic extremity is handled will determine whether amputation will be avoided. The author's conservative method of handling such tissue, based on a large experience, should go far to elevate this phase of the management of the patient with gangrene to its proper importance. One might disagree, however, with several of the author's opinions on the general management of the patient with thromboangiitis obliterans and arteriosclerosis. For example, the author's belief that sympathectomy and paravertebral block offer very little to these patients is not in accord with the clinical experience of others who have used these procedures with benefit to many patients. Also, the author's emphasis on the use of hypertonic saline does not seem to be borne out by the experience of others. On the whole, however, this is a good book from the clinical standpoint on the management of the patient with thromboangiitis and arteriosclerosis obliterans.

MEYER NAIDE

Current Therapy 1950. Latest Approved Methods of Treatment for the Practicing Physician. *Howard F. Conn,* ed. W. B. Saunders and Company, Philadelphia and London, 1950. 736 pages, $10.00.

Section Three of the second edition devotes 48 pages to 29 articles by 16 authors on diseases of the cardiovascular system. Two or three independent discussions are provided for eight of the 18 subjects, including congestive failure, hypertension, the anginal syndrome, coronary occlusion and rheumatic heart disease. Peripheral vascular disease is covered in fragmentary fashion by four short articles which are below the standards of many of the others.

All presentations are handicapped by limitation of the subject matter to treatment without relating this to basic pharmacology and physiology. Diagnostic criteria are seldom described. While in accord with the stated purposes of the volume as a whole, this method is not well suited to diseases of the circulation. Nevertheless the articles provide considerable information about accepted and tentative therapy of heart disease and hypertension some of which has not yet found its way into textbooks of medicine.

A series of annual cumulative revisions are planned for this book. A few references to pertinent material in generally available journals might increase its value to the physician not closely in touch with new developments in the cardiovascular field.

JOHN J. SÄYEN

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TRAINING FOR CARDIOVASCULAR INVESTIGATORS

The Association has approved a grant-in-aid in the amount of $18,270 toward the continuance of the Training Course for Cardiovascular Investigators at Western Reserve University, Cleveland. The course is directed by Dr. Carl J. Wiggers, Professor and Director, Department

of Physiology, at the University's Medical School. The third year will begin on July 1, 1951.

The course was inaugurated in 1949 as a means of increasing the number of competent research investigators in the cardiovascular field. The chief objective was to give a year's training to postdoctorate fellows in medicine and related sciences. It was set up through the support of the Association.

The Research trainees are supported by the National Heart Institute and carry an annual stipend of $3,000 to $3,600 per annum, depending on the candidate's dependency status.

The current program, to be continued during 1951–52, consists of eight weeks of formalized technical training in various research methods employed in cardiovascular studies on humans and animals, 18 weeks of experimentation apprenticeship involving the assistance of qualified investigators in basic animal research, 16 weeks of independent research under supervision, and six weeks of supervised experience in the preparation of a manuscript.

COUNCIL ON HIGH BLOOD PRESSURE RESEARCH

The annual meeting of the Council on High Blood Pressure Research will be held on April 6 and 7 in Cleveland at the Hotel Cleveland. The Council is composed of physicians and lay members interested in problems of high blood pressure and arteriosclerosis. Many prominent business leaders have been invited to attend its sessions.

Mr. Alva Bradley, Chairman of the Council's Medical Advisory Board, will serve as Chairman for the meeting. Reports on progress, current needs, and the outlook in this field will be given by Dr. Irvine H. Page, Cleveland, Dr. Louis N. Katz, Chicago, and Dr. Henry A. Schroeder, St. Louis.

TRAINING OF LABORATORY TECHNICIANS

A program for the training of laboratory technicians in the correct technics for accurate prothrombin and clotting time tests has been inaugurated at the Newton-Wellesley Hospital, Newton, Mass. This is a joint effort sponsored by the Health Department of Massachusetts and the local physicians of the community, with the full cooperation of the Massachusetts Heart Association and the United States Public Health Service.

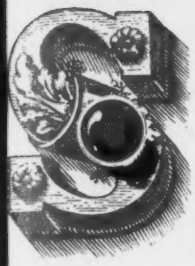
The course was initiated last July under the technical direction of Dr. Irving S. Wright, Chairman of the Committee on Anticoagulants of the American Heart Association. Dr. Ralph Overman has acted as Consultant in Chemistry. Arrangements were made whereby technicians from hospitals of Massachusetts came to the Newton-Wellesley Hospital for a period of five days during which they received actual practical training in these determinations. Four technicians were trained each week. To date, 64 technicians, representing 50 different hospitals and laboratories have been trained.

This was a pilot program. Preparations for the development of similar programs in communities where there is an interest and desire for training of this nature are being made.

INTERNATIONAL SOCIETY OF CARDIOLOGY

Dr. Louis N. Katz, Chicago, has been appointed as the Association's second delegate to the Council of the newly-organized International Society of Cardiology (Heart and Blood Vessels). Dr. Maurice B. Visscher, Minneapolis, has been named as alternate for Dr. Paul D. White, Boston, first delegate to the Council. Dr. Edgar V. Allen, Rochester, Minn., has been named as alternate for Dr. Katz.

The Officers of the International Society are: Professor Charles Laubry, Paris, President; Dr. Paul D. White, Boston, First Vice-President; Professor Ignacio Chavez, Mexico City, Second Vice-President; Dr. Pierre W. Duchosal, Geneva, Secretary General; Dr. Pedro Cossio, Buenos Aires, Associate Secretary; Professor Gustav Nylin, Stockholm, Treasurer; and Dr. Louis N. Katz, Chicago, Assistant Treasurer.



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